WYETH-AYERST RESEARCH

May 19, 1988

Dr. Bonnie M. Davis
17 Seacrest Drive
Huntington, New York 11743

Dear Dr. Davis:

Thank you for your letter of April 29th, 1988. I forwarded your letter to Dr. Eric Muth, head of the CNS Subdivision at Wyeth-Ayerst. He informed me that his CNS group had already reviewed your materials a few months ago, and they did not express interest in this product. There is still skepticism regarding the success of cholinesterase inhibitors in the treatment of senile dementia.

In the event of new encouraging data becoming available in the future, Wyeth-Ayerst may re-open discussions with you.

Thank you for giving me the opportunity to review your materials.

Best regards.

Sincerely,

MAG:mw

Magid Abou-Gharbia, Ph.D.
Assistant Director
Medicinal Chemistry

cc: Dr. Muth
Dr. Cressman
Dr. Jensen
Dr. Yardley

CN 8000, PRINCETON, NJ 08543-8000 • TELEPHONE (201) 329-2300
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Plaintiff's Exhibit
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LTH-338

EXHIBIT 14

LICENCE

THIS AGREEMENT is made the 30 day of November 1995

BETWEEN:-

(1) **SYNAPTECH INC** a company organised and existing under the laws of the State of New York whose principal place of business is c/o Schwartz & Salomon, 42nd Floor, 225 Broadway, New York 10007-3001 USA ("Synaptech"); and

(2) **JANSSEN PHARMACEUTICA NV** a Belgian business corporation organised and existing under the laws of Belgium with its registered office at Turnhoutseweg 30, B-2340 Beerse, Belgium ("Janssen").

RECITALS:-

(A) Synaptech is the beneficial owner of all the rights, title and interest in the Patent and has access to the Synaptech Know-how.

(B) Synaptech is willing to grant to Janssen, and Janssen is willing to accept, an exclusive licence under the Patent and the Synaptech Know-how to develop, make, have made, keep, use, market, sell and/or dispose of the Licensed Product throughout the Janssen Territory in accordance with the provisions of this Agreement.

IT IS AGREED AS FOLLOWS:-

1. DEFINITIONS

1.1 In this Agreement the following words shall have the following meanings, unless the context requires otherwise:-

"Affiliate"	(1) any corporation or other business entity owning or directly or indirectly having effective control over the activities of a party to this Agreement or (2) any corporation or other business entity that is directly or indirectly controlled by a party to this Agreement or (3) any corporation or other business entity that is directly or indirectly controlled by any corporation or business entity that directly or indirectly has effective control of a party to this Agreement;

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Plaintiff's Exhibit
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"Ciba Data"	the full and complete data and related summaries and documentation generated by the Ciba Geigy study MIN Number 921003 Rat 26/52 week and study MIN Number 921004 Dog 26/52 week;
"Commercial Delivery"	the first sale to a third party customer for commercial use of any Licensed Product in a country of the Janssen Territory after the grant of Product Approval in that country;
"Customers"	any third party, other than an Affiliate or Sublicensee of Janssen, to whom Janssen, its Affiliates or Sublicensees sell the Licensed Product;
"Galanthamine"	galanthamine or pharmaceutically acceptable acid addition salts thereof;
"Improvements"	any new technique or formulation or the new application of an old technique or formulation relating to the use of Galanthamine for the treatment of Alzheimer's disease and related dementias. For the avoidance of doubt it excludes techniques and formulations relating to the manufacture or production of Galanthamine and data arising out of the development of the Licensed Product;
"Janssen Territory"	the United States of America, Canada, Mexico, The Republic of Korea, Taiwan, Thailand and Singapore;
"Know-how Royalty Rate"	the royalty rate as specified in Clause 5.1.7;
"Licensed Product"	any product containing Galanthamine sold by Janssen, its Affiliates or Sublicensees which is used for or intended to be used for the treatment of Alzheimer's disease and related dementias in the Janssen Territory;
"Net Sales Value"	the amount billed or invoiced by Janssen, its Affiliates or Sublicensees to Customers for sales of Licensed Product in the Territory less freight, sales taxes, trade or ordinary discounts, government rebates and amounts repaid or credited because of return of goods;

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"NDA"	NDA shall mean a New Drug Application and all supplements filed pursuant to the requirements of the FDA, including all documents, data and other information concerning the Licensed Product which are necessary for or included in, FDA approval to market the Licensed Product as more fully defined in 21. C.F.R. §314.5 et seq;
"Patent"	United States Patent 4,663,318 or any extension thereof;
"Patent and Know-how Royalty Rate"	the royalty rate as specified in Clause 5.1.7;
"Permitted Transferee"	Dr. Bonnie Davis, her heirs, any one or more members of her family or any entity set up for her benefit or that of her family or any part thereof or her heirs;
"Major Countries"	the countries listed in Schedule 1;
"Product Approval"	the grant of all necessary governmental and regulatory approval to sell the Licensed Product in any country of the Janssen Territory including without limitation acceptable pricing and reimbursement;
"Quarter"	Janssen's standard quarter periods ending around March, June, September and December;
"Reduced Know-how Royalty Rate"	the royalty rates as specified in Clause 5.1.7;
"Shire"	Shire Holdings Limited a company organised and existing under the laws of Bermuda and any Affiliate thereof;
"Shire-Janssen Sub-Licence Agreement"	the sub-licence granted to Janssen by Shire under the terms of Shire's Agreement with Synaptech made the same date as this Agreement;
"Sublicensee"	means a sublicensee appointed pursuant to Clause 2.4

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"Synaptech Know-how"	information in Synaptech's possession or under its control and which it is free to disclose prior to or during the term of this Agreement relating to the use of Galanthamine in the treatment of Alzheimer's disease and related dementias including but not limited to all technical information arising from all in vitro, in vivo studies and data conducted on behalf of Synaptech and which relates to using Galanthamine for the treatment of Alzheimer's disease and related dementias which information is supplied to Janssen prior to or during this Agreement;
"Synaptech Analogues"	analogues of Galanthamine claimed in any granted patents which (1) are owned by Synaptech, its Affiliates or Dr Bonnie Davis and (2) were filed before the date of this Agreement or claim priority from an application filed before the date of this Agreement.

2. GRANT OF LICENCE

2.1. Synaptech grants to Janssen an exclusive licence under the Patent and the Synaptech Know-how to develop, make, have made, keep, use, sell and/or dispose of the Licensed Product in the Janssen Territory. Janssen shall have the right to grant sub-licences subject to Clause 2.4.

2.2 Synaptech grants to Janssen a licence and shall procure the grant of a licence from any Affiliate or from Dr Bonnie Davis to Janssen under any other intellectual property rights owned by Synaptech or an Affiliate or Dr Bonnie Davis to the extent but only to the extent that such a licence may be necessary to enable Janssen using any synthetic process to manufacture synthetic Galanthamine whether for Alzheimer's disease and related dementias or for any other indications . For the avoidance of doubt it is agreed that this licence includes a licence to make or have made any analogue of Galanthamine that may be an intermediate in the synthesis of Galanthamine. Janssen will inform Synaptech whenever the final synthesis involves an intermediate claimed in the current patents or patent applications owned by Synaptech, its Affiliates or Dr Bonnie Davis. Any such disclosure by Janssen shall be limited to the identification of such intermediate. In no event shall Janssen be obliged to disclose the synthesis process for Galanthamine.

2.3 Subject to Clause 4 Synaptech shall grant to Janssen an exclusive license to use the Ciba Data for Galanthamine for use in the treatment of Alzheimer's disease and related dementias and for use in other indications throughout the Janssen Territory.

2.4 Janssen shall have the right to grant sublicenses other than in the United States of America (provided that Janssen shall have the right to appoint a co-marketing partner in the United States of America) hereunder on terms not inconsistent with this

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Agreement and containing obligations on the Sublicensee analogous to those of Clauses 5-12, 16 and 17 hereof. Before appointing a Sublicensee, Janssen shall consult with Synaptech and take into account its comments and suggestions relating to any proposed Sublicensee. Janssen shall not appoint a Sublicensee without Synaptech's consent (such consent not to be unreasonably withheld) provided that Janssen shall be free to appoint an Affiliate as a Sublicensee without Synaptech's consent. Janssen shall, within ninety (90) days of the final execution of any such sublicense, furnish to Synaptech a copy of each such sublicense granted to third parties hereunder. Janssen shall report to Synaptech the sales of Sublicensee in the same manner and form in which it must report its own sales but will on request by Synaptech provide Synaptech with a statement by independent auditors appointed by Janssen and reasonably acceptable to Synaptech confirming the accuracy of the reports submitted to Synaptech.

2.5 Synaptech agrees to execute such formal licences and other documents as Janssen considers may be necessary or appropriate from time to time for registration with Patent Offices and/or other relevant authorities. In the event of any conflict in meaning between any such formal licence and the provisions of this Agreement, the provisions of this Agreement shall prevail. Synaptech and Janssen shall use their reasonable endeavours to ensure that, to the extent permitted by relevant authorities, this Agreement shall not form part of any public record.

3. INITIAL AND MILESTONE PAYMENTS

3.1 Initial Payment

Within 7days of the date of this Agreement, Janssen shall pay to Synaptech in full without any deductions whatsoever the non-refundable sum of US$1,600,000 (US Dollars) to a bank account designated in writing by Synaptech.

3.2 Milestone Payments

Janssen shall pay to Synaptech in full without any deductions whatsoever the following non-refundable sums:-

3.2.1 US$400,000 (US Dollars) within 30 days of the submission of the NDA for Licensed Product with the FDA in the United States of America;

3.2.2 US$450,000 (US Dollars) within 30 days of the approval of the NDA for Licensed Product by the FDA.

4. CIBA DATA

4.1 Synaptech shall use all reasonable endeavours to negotiate with Ciba Geigy the lowest possible price for the transfer of the Ciba Data to Synaptech. Synaptech shall notify Janssen of such price forthwith upon agreeing the price with Ciba Geigy.

4.2 The sums set out in Clauses 4.5.1 and 4.6 have been calculated on the assumption that the price for the transfer of the Ciba Data to Synaptech for global use (including Japan)

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will be US$ 1,800,000. If Synaptech succeeds in reducing this price pursuant to Clause 4.1 then the sums set out in Clauses 4.5.1 and 4.6 shall be reduced in proportion with the reduction in the price.

4.3 Janssen shall notify Synaptech prior to the filing of an Investigational New Drug ("IND") application for Licensed Product in the United States as to whether or not it requires the Ciba Data.

4.4 If Janssen notifies Synaptech that it does not require the Ciba Data the provisions of Clause 2.3 and Clauses 4.2-4.6 inclusive shall cease to apply.

4.5 If Janssen notifies Synaptech that it does require the Ciba Data then within 14 days of such notification:

4.5.1 Janssen shall pay to Synaptech US$ 1,202,000 (US dollars) in consideration for the license granted under Clause 2.3; and

4.5.2 Synaptech shall supply to Janssen a complete copy of the Ciba Data.

4.6 Synaptech shall repay to Janssen US$300,000 (US dollars) in respect of the use of Ciba Data in Japan in accordance with the following provisions:—

4.6.1 Janssen shall be entitled to deduct US$150,000 (US dollars) from the first milestone payment due to Synaptech under Clause 3.2.1 and the remaining US$150,000 (US dollars) (if not already repaid under Clause 4.6.2) from the royalty payments due to Synaptech under Clause 5.

4.6.2 If Synaptech appoints a licensee to market and sell Galanthamine for use in the treatment of Alzheimer's disease and related dementias in Japan under its patents or patent applications then forthwith upon such appointment Synaptech shall repay to Janssen US$ 300,000 (US dollars).

4.7 Subject to Clause 4.8, except as hereinafter provided Synaptech and Janssen shall, and shall procure that their respective directors, officers and employees, shall keep the Ciba Data strictly confidential and shall not disclose the Ciba Data to any third party other than a prospective licensee or a licensee appointed by Synaptech to market and sell Galanthamine in Japan. It is acknowledged that disclosure of the Ciba Data has been made by Synaptech solely for academic purposes to a third party and Synaptech shall procure that no publication of the Ciba Data shall be made by such third party without Janssen's prior written consent such consent not to be unreasonably withheld. Synaptech shall not and shall procure that its directors, officers and employees shall not use the Ciba Data for any purpose within the Janssen Territory. However, it is understood that Janssen shall be entitled to use and disclose the Ciba Data in accordance with the provisions of Clause 11.4

4.8 In the event that Synaptech wishes to use the Ciba Data in connection with an indication other than in the treatment of Alzheimer's disease or related dementias Janssen shall permit such use.

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5. **ROYALTY**

5.1 Amount of Royalty

5.1.1 Janssen shall pay to Synaptech, subject to Clause 5.1.4, the Patent and Know-how Royalty Rate on the Net Sales Value of all Licensed Product sold by Janssen, its Affiliates or sublicensee in any country of the Janssen Territory where a Patent remains in force in such country.

5.1.2 Janssen shall pay to Synaptech, subject to Clause 5.1.5, the Know-how Royalty Rate on the Net Sales Value of all Licensed Product sold by Janssen, its Affiliates or Sublicensee in any country of the Janssen Territory where a Patent has ceased to be in force. Such royalty shall be payable for a period of ten years following the date upon which the Patent ceased to be in force in such country.

5.1.3 Janssen shall pay to Synaptech, subject to Clause 5.1.5, the Know-how Royalty Rate on the Net Sales Value of all Licensed Product sold by Janssen, its Affiliates or Sublicensee in any country of the Janssen Territory where at the date of this Agreement there is no Patent in force. Such royalty shall be payable for a period of ten years from the date of the first Commercial Delivery of Licensed Product in such country.

5.1.4 If in a country of the Janssen Territory where there is a Patent in force and one or more third parties (other than Affiliates or Sublicensees) sell pharmaceutical products containing Synaptech Analogues which compete directly with the Licensed Product and such competing products take more than 20% by value of sales of the Licensed Product in that country for two consecutive Quarters then in respect of that country only the Know-how Royalty Rate shall apply instead of the Patent and Know-how Royalty Rate for as long as such competing products take more than 20% by value of sales of the Licensed Product in that country; or

5.1.5 If in a country of the Janssen Territory where there is no Patent in force one or more third parties (other than Affiliates or Sublicensees) sell pharmaceutical products containing Galanthamine or Synaptech Analogues which compete directly with the Licensed Product and such competing products take more than 20% by value of sales of the Licensed Product in that country for two consecutive Quarters then in respect of that country the Reduced Know-how Royalty Rate shall apply instead of the Know-how Royalty Rate for as long as such competing products take more than 20% by value of sales of the Licensed Product in that country.

5.1.6 For the avoidance of doubt the royalty rates referred to in Clauses 5.1.4 and 5.1.5 above shall apply in respect of the third Quarter in which the competing products take more than 20% by value of sales of the Licensed Product in the country concerned. In succeeding Quarters the Know-how Royalty Rate or the Reduced Know-how Royalty Rate (as applicable) shall apply until a Quarter is reached when such competing products after two consecutive

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Quarters no longer take more than 20% by value of sales of the Licensed Product in the relevant country in which case the Know-how Royalty Rate or the Reduced Know-how Royalty Rate (as applicable) shall apply to that Quarter but the Patent and Know-how Royalty Rate or the Know-how Royalty Rate (as applicable) shall apply to succeeding Quarters.

5.1.7 The Patent Royalty Rate, the Know-how Royalty Rate and the Reduced Royalty Rate are set out below:-

Patent and Know-how Royalty Rate	Know-how Royalty Rate	Reduced Know-how Royalty Rate
5%	3%	2%

5.1.8 Royalties payable under this Clause 5.1 are subject to the apportionment (if any) of Net Sales Value in accordance with the provisions of Clause 7.3

5.1.9 For the avoidance of doubt in no circumstances shall Janssen be obliged to pay a royalty under both Clause 5.1.2 and Clause 5.1.3 in respect of the same sales of Licensed Product .

5.1.10 Subject to Clause 7.3, nothing to the contrary in this Agreement shall require Janssen to pay royalties in respect of any sales by Janssen, its Affiliates or sublicensees of Galanthamine for use in indications other than the treatment of Alzheimer's disease and related dementias in any country of the Janssen Territory other than those explicitly provided for in this Agreement.

5.2 Frequency of Payment

Royalties due under this Clause 5 shall be payable to a bank account designated in writing by Synaptech within 45 days of the end of each Quarter in respect of sales of the Licensed Product made during such Quarter.

5.3 Combination Products

Janssen and its Affiliates shall not sell the Licensed Product in combination with any other compound, drug delivery system, materials, equipment or apparatus without the parties having first agreed upon what proportion of the total selling price of the combination product should be attributable to the Licensed Product. The parties shall in each case use their reasonable endeavours to negotiate in good faith a fair and reasonable proportion. If the parties fail to agree a proportion within 90 days then either party shall be entitled to refer the matter for resolution pursuant to Clause 19.11.

5.4 Sales which are not made on an "arms length" basis

5.4.1 If Janssen or its Affiliates sells the Licensed Product to any Customer other than on an "arm's length" commercial basis, the Net Sales Value of such Licensed Product shall be which ever is the higher of:-

5.4.1.1 the fair market value of such Licensed Products; or

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5.4.1.2 the actual price at which Janssen or its Affiliate sold the Licensed Products to such Customer.

5.4.2 If Janssen or its Affiliates sells the Licensed Product to any Customer as part of package of products then the Net Sales Value of the Licensed Product shall be which ever is the higher of:-

5.4.2.1 the fair market value of the Licensed Product when sold by itself or

5.4.2.2 the proportion of the package price attributed to the Licensed Product by Janssen or its Affiliates and the Customer.

5.4.3 This Clause 5.4 shall be without prejudice to Janssen and its Affiliates' right to offer ordinary trade discounts in accordance with its normal business practices and for the purposes of Clause 5.4 fair market value shall mean, without limitation, the value of Licensed Product sold to similar Customers in countries with similar pricing and reimbursement structures and for similar quantities. Any dispute as to the determination of fair market value that cannot be resolved through discussion between the parties shall be referred for resolution pursuant to Clause 19.11.

6. PAYMENT TERMS

6.1 All sums due under this Agreement:-

6.1.1 Are exclusive of any Value Added Tax, or other sales taxes or duty which where applicable will be payable by Janssen to Synaptech in addition.

6.1.2 Shall be made in US dollars to the credit of a bank account designated in writing by Synaptech. If the Licensed Product is sold or supplied by Janssen or its Affiliates in a currency other than US dollars the Net Sales Value shall first be determined in the currency in which such Licensed Product was sold or supplied and then converted into equivalent US dollar at the middle market rate of such foreign currency as quoted by the London Financial Times as at the close of business of the last business day of the Quarter with respect to which the payment is made.

6.1.3 Shall be made in full without deduction of income or other taxes, charges and/or duties that may be imposed except insofar as Janssen is required to deduct the same to comply with relevant laws. In the event that Janssen is required to make any such deduction it shall promptly provide Synaptech with a certificate or other documentary evidence sufficient to enable Synaptech to support a claim for a tax credit in respect of any amount so withheld. In case Synaptech cannot take a full credit against its tax liability for the withholding tax deducted or withheld by Janssen then Janssen may propose a change to the then current arrangement with respect to the flow of monies under this Agreement in order to reduce or eliminate the cost to Synaptech. The

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preceding provision shall not be applicable in case Synaptech cannot take a full credit against its tax liability for the withholding tax due to Synaptech's negligence to comply with all legal and other requirements necessary to claim such tax credit.

6.1.4 Shall be made by the due date for payment as provided in this Agreement failing which Synaptech, without prejudice to any other right or remedy available to Synaptech under this Agreement, shall notify Janssen as to any payment overdue for 14 days and Janssen shall pay interest on such outstanding amount overdue on a daily basis at a rate equivalent to LIBOR (6 month rate) plus 2 per cent .

6.2 Prohibitions on Payment

6.2.1 If at any time during the continuation of this Agreement Janssen is prohibited from making any of the payments required hereunder by a governmental authority then Janssen will within the prescribed period for making the said payments in the appropriate manner use its reasonable endeavours to secure from the proper authority in the relevant country permission to make the said payments and will make them within thirty (30) days receiving such permission.

6.2.2 In the event that such permission is not received within thirty (30) days of Janssen making such a request for permission Janssen shall deposit the royalty payments due in a bank account designated by Synaptech within the relevant country.

7. RECORDS AND REPORTS

7.1 Maintain Records

7.1.1 Janssen and its Affiliates shall keep at their normal place of business detailed, accurate and up to date records and books of account showing the quantity, description and value of the Licensed Product sold by Janssen and its Affiliates in each country within the Janssen Territory during the previous two (2) years and being sufficient to ascertain the royalties payable during the term of this Agreement and for one (1) year thereafter.

7.1.2 Having been given ten (10) working days notice by Synaptech, Janssen shall make such records and books available for inspection at all reasonable times during business hours not more than twice in any calender year by Synaptech or an independent auditor appointed by Synaptech for the purpose of verifying the accuracy of any statement or report given by Janssen to Synaptech and/or the amount of royalties due and any such representatives making such inspection shall be entitled to take copies or extracts from Janssen records and books of account.

7.1.3 Synaptech and/or the independent auditor appointed under Clause 7.1.2 shall maintain all such information and materials in strict confidence.

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7.1.4 Synaptech shall be solely responsible for its costs in making such inspections unless there is a material inaccuracy that is a deficit greater than 5 per cent on any royalty statement in which event Janssen shall forthwith pay to Synaptech the costs in making the relevant inspections make good the deficit and pay interest on the deficit at LIBOR (6 month rate) plus 2 per cent.

7.2 Royalty Statements

Janssen shall send to Synaptech at the same time as each royalty payment is made under Clause 5.2 above a statement:-

7.2.1 setting out in respect of each country in which Licensed Product is supplied to a Customer by presentation form the quantity and Net Sales Value of Licensed Product sold and supplied free of charge during the Quarter to which the royalty payment relates. The statement shall show the total Net Sales Value expressed both in local currency and in US dollars, showing the conversion rate used; and

7.2.2 showing for each country in which the Licensed Product is sold the applicable royalty rate used and the calculation of the royalties payable pursuant to Clause 5.1.

7.3 Apportionment of Net Sales Value between Alzheimer's disease and Chronic Fatigue Syndrome

Janssen and Synaptech are aware that a difficulty exists throughout the Janssen Territory in determining whether Galanthamine has been used for the treatment of Alzheimer's disease and related dementias or for the treatment of Chronic Fatigue Syndrome ("CFS") in respect of which Janssen and Shire have entered into a separate agreement . Janssen and Synaptech have determined to resolve this problem in the Janssen Territory in the following manner:-

7.3.1 Janssen will make reasonable efforts to report to Synaptech for each country of the Janssen Territory sales of Galanthamine for (1) Alzheimer's disease and related dementias and (2) CFS and shall report the same on a confidential basis on the first day of January and the first day of July in each year within 60 days of each such date in each year.

7.3.2 In any country of the Janssen Territory where only one of either (1) Licensed Product has been granted a Product Approval ("Alzheimer's approval") or (2) where all necessary governmental or regulatory authority (including without limitation acceptable pricing and reimbursement) to sell Galanthamine for the treatment of CFS has been granted ("CFS approval") then all sales of Galanthamine in that country of the Janssen Territory shall be attributed to either (1) Licensed Product if Alzheimer's approval has been obtained or (2) CFS if CFS approval has been obtained. Upon the date that both Licensed Product has been granted a Product Approval and CFS approval have been granted then Clause 7.3.3 below shall apply.

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7.3.3 Janssen and Synaptech agree that to establish the percentage proportion of sales of Galanthamine in any country of the Janssen Territory for the purpose of calculating royalty payments applicable to Synaptech for Alzheimer's disease and related dementias and to the third party holder of patent rights covering the use of Galanthamine in the treatment of CFS ("the proportion") that patients of the age of 50 and over shall be deemed to have Alzheimer's disease and related dementias and patients under 50 years shall be deemed to have CFS.

7.3.4 If either party reasonably believes that a more accurate method of calculation of the proportion set out in Clause 7.3.3 has become available it will consult with the other in an effort to amend this clause appropriately in consultation with Shire. If no agreement can be reached within 6 weeks then either party shall have the right by serving notice in writing on the other to refer the matter for resolution pursuant to Clause 19.11.

7.3.5 Notwithstanding anything to the contrary in this Agreement in no circumstances whatsoever shall Janssen be required to pay royalties in respect of any sales by Janssen or its Affiliates of Galanthamine in any country of the Janssen Territory to both (1) Synaptech and (2) the third party holder of patent rights covering the use of Galanthamine in the treatment of CFS.

8. DEVELOPMENT, LAUNCH, COMMERCIALISATION AND PRODUCT LIABILITY

8.1 Janssen Development

8.1.1 Janssen shall use reasonable efforts consistent with its normal business practices to carry out the development activities directed to Licensed Product with the aim of developing Licensed Product that can be commercialised. Such level of effort will be consistent with the level of effort used by Janssen in connection with other products of Janssen of similar importance (based on such criteria as patient population, price per treatment and competitive position). Janssen shall supply Synaptech at least once every Quarter with a report on the status of the development of the Licensed Product. Janssen shall use reasonable efforts consistent with its normal business practices to make Product Approval applications in the Major Countries in accordance with the timetable set out in Schedule 2. Janssen advise that as at the date hereof the development of the use of Galanthamine for treatment of Alzheimer's disease is significantly more advanced than the development for other indications such as CFS. Janssen envisages as at the date of this Agreement that the use of its reasonable efforts as stated above (taking account of the anticipated requirements of the drug regulatory authorities requirements for drugs for the treatment of Alzheimer's disease and CFS) should lead to the filing of submissions for Product Approvals in the Major Countries for the use of Galanthamine for treatment of Alzheimer's disease prior to filing of applications (if any) for the use of Galanthamine for the treatment of CFS.

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8.1.2 If in any Major Country the application for Product Approval is refused then the parties will discuss a potential course of action. In no event will Janssen's rights in such Major Country be terminated for breach of this Clause 8.1, unless in the opinion of an arbitrator appointed in accordance with Clause 19.11 the refusal of Product Approval is considered to be caused by Janssen's breach of its obligations under this Clause in filing and supporting such application at which moment Synaptech can terminate Janssen's rights in such Major Country in accordance with Clause 16.2.3.

8.2 Janssen's Launching and Marketing Efforts

8.2.1 All business decisions, including but not limited to, pricing, reimbursement, package design, sales and promotional activities and the decision to launch or keep a Licensed Product on the market in a particular country, shall be within the sole discretion of Janssen.

8.2.2 Without prejudice to generality of the foregoing, it is agreed with respect to each of the Major Countries that Janssen will launch the Licensed Product within six (6) months after obtaining Product Approval in such Major Country. Such six (6) months period will be extended whenever Janssen reasonably requests so for sound business reasons, such as but not limited to the launch by Janssen or its Affiliates of other Janssen products in such Major Countries or the intended simultaneous launch of Licensed Product in several countries. Janssen will promptly inform Synaptech of the date of launch of the Licensed Product in each of the Major Countries and will regularly update Synaptech on the launch of the Licensed Product in other countries. Janssen agrees to use reasonable efforts to promote and market the Licensed Product in a Major Country after launch in such Major Country. Such level of effort will be consistent with the level of effort used by Janssen in connection with other products of Janssen of similar importance (based on such criteria as patient population, price per treatment and competitive position).

9. PATENTS

9.1 Maintain Patents

9.1.1 Synaptech shall pay the renewal fees for the Patent and all costs incurred by Synaptech in this regard after the date of this Agreement shall be reimbursed by Janssen within 30 days of the date of receipt of an invoice from Synaptech in respect of such costs.

9.1.2 The parties agree to cooperate in order to avoid loss of any rights which may otherwise be available to the parties under the US Drug Price Competition and Patent Term Restoration Act of 1984 and other similar measures in any other country in the Janssen Territory. Without limiting the foregoing, Janssen agrees to notify Synaptech promptly upon receipt of an NDA approval to market Licensed Product in the United States and to timely supply Synaptech with all information necessary to file an application for patent term extension within the sixty (60) day period following NDA

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approval. The same shall apply with respect to the approval by the health authorities in any other country in the Janssen Territory.

9.2 Infringement of the Patent

9.2.1 Janssen and Synaptech shall notify each other forthwith in writing of any infringement or suspected or threatened infringement of the Patent by the use and sale of products containing Galanthamine for the treatment of Alzheimer's disease and related dementias which shall at any time come to their knowledge. Such notice shall include any information concerning the infringement which is known to the party giving notice at the date of the notice establishing a prima facie case of infringement by such third party.

9.2.2 In the event that such infringement or threatened infringement constitutes a substantial infringement, Janssen shall take action to stop such infringement of the Patent including without limitation conducting patent infringement proceedings or starting settlement discussions in its own name and own cost and by counsel of its own choice. For the purposes of this Clause 9.2.2 the expression, substantial infringer, shall mean an infringer of the Patent as defined in Clause 9.2.1 that takes or is likely to take more than ten (10) per cent by value of sales of the Licensed Product in the United States of America. Notwithstanding the above provisions Janssen shall not be obliged to start any such action whenever in the opinion of an independent patent counsel selected by Janssen after notification to Synaptech to whom Synaptech shall reasonably have no major objection (a copy of which shall be supplied to Synaptech) the chances of prevailing in any such action are minimal.

9.2.3 Synaptech shall provide to Janssen such assistance as Janssen may reasonably request in connection with proceedings against infringers of the Patent (subject to the reimbursement of its out of pocket expenses, including reasonable attorney's fees, incurred in connection therewith) including without limitation:

9.2.3.1 making available to Janssen such records, information and evidence in its possession or control which may be of assistance to Janssen; and

9.2.3.2 giving Janssen the authority to file and prosecute proceedings against infringers of the Patent; and

9.2.3.3 giving Synaptech's consent to be named as a party in any proceedings against infringers of the Patent.

9.2.4 Janssen shall keep Synaptech regularly informed of the progress of and developments in, any proceedings against infringers of the Patent including any settlement discussions with such infringers. Without prejudice to Clause 9.2.5, Synaptech shall be entitled to promptly comment on any such

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development, it being understood that in no event shall such entitlement delay any proceedings.

9.2.5 Janssen shall have full control of the conduct of any proceedings it initiates against infringers of the Patent.

9.2.6 Janssen may negotiate settlement with an infringer of the Patent but shall not conclude any such settlement without Synaptech's prior written approval of the terms of the settlement, such approval not be unreasonably withheld or delayed.

9.2.7 Janssen shall be entitled to apply up to 50% of each Quarter's royalties otherwise payable to Synaptech under Clause 5 in respect of the United States of America to cover its reasonable out of pocket expenses incurred by Janssen or its designated Affiliate in bringing infringement proceedings under the Patent and subject as aforesaid shall be recoverable in full during the course of its obligation to pay royalties under Clause 5.

9.2.8 If both of the following conditions are met:

9.2.8.1 Janssen after having started action in accordance with Clause 9.2.2 fails to stop the infringing activities within 180 days of the date on which the infringement was notified pursuant to Clause 9.2.1; and

9.2.8.2 products which infringe the Patent take more than 20% by value of sales of the Licensed Product for two consecutive Quarters in the United States of America;

then in respect of the United States of America only the Know-how Royalty Rate shall apply for as long as products infringing the Patent take more than 20% by value of sales of the Licensed Product in the United States of America.

9.2.9 Any damages, costs, awards or other sums received by Janssen arising out of any proceedings brought by Janssen for infringement of the Patent (or the settlement of any such proceedings) shall be divided between the parties in the following order of priority:

9.2.9.1 Janssen shall be entitled to its reasonable out of pocket expenses actually incurred by Janssen or its designated Affiliate in respect of the proceedings for infringement of the Patent insofar as such expenses have not already been deducted from the royalties payable to Synaptech pursuant to Clause 9.2.7;

9.2.9.2 Synaptech shall be entitled to a sum equal to any royalties withheld pursuant to Clause 9.2.7; and

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9.2.9.3 Janssen shall be entitled to retain the remainder subject to the payment by Janssen to Synaptech of the Patent and Know-how Royalty Rate on the remainder as if the remainder had been included in the Net Sales Value.

9.2.10 Synaptech hereby releases, disclaims and otherwise holds harmless Janssen from and against any claim Synaptech may have other than those arising from gross negligence for damages arising out of such enforcement proceedings including without limitation a finding of invalidity of the Patent.

9.2.11 If for any reason Janssen fails to take action against any infringer of the Patent within 90 days of being notified of such infringement then Synaptech may take proceedings against such infringer and Janssen shall promptly provide Synaptech with such assistance as Synaptech may reasonably request (subject to the reimbursement of its out of pocket expenses, including reasonable attorney's fees, incurred in connection therewith) including without limitation making available to Synaptech, records, information and evidence relevant to the infringement. In that case Synaptech shall be entitled to retain 100% of any damages recovered. If both the following conditions are met:

9.2.11.1 Synaptech after having started action in accordance with this Clause 9.2.11 fails to stop the infringing activities within 180 days of the date on which the infringement was notified pursuant to Clause 9 2.1; and

9.2.11.2 products which infringe the Patent take more than 20% by value of sales of the Licensed Product for two consecutive Quarters in the United States of America.

then in respect of the United States of America only the Know-how Royalty Rate shall apply as long as products infringing the Patent take more than 20% by value of sales of the Licensed Product in the United States of America.

9.2.12 Synaptech shall be entitled to recover any damages, costs, awards or other sums received by it arising out of any proceedings brought by Synaptech for infringement of the Patent or the settlement of any such proceedings.

9.3 Infringement of Third Party Rights

9.3.1 If the use and/or sale of Galanthamine for the treatment of Alzheimer's disease and/or related dementias constitutes an infringement of the rights of a third party in a country of the Janssen Territory, each party shall, as soon as it becomes aware of such infringement, notify the other party thereof in writing giving in the same notice full details known to it of the rights of such third party and the extent of any potential infringement.

9.3.2 The parties shall after receipt of such notice referred to in Clause 9.3.1 above discuss the situation and to the extent necessary attempt to agree a course of

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action in order to permit Janssen to practice the licences granted under this Agreement. Such course of action may include (a) obtaining an appropriate licence from such third party; or (b) contesting any claim or proceedings bought by the third party.

9.3.3 If within 21 days the parties fail to agree upon an appropriate course of action the party being sued may decide upon the course of action in the interest of further development and/or commercialisation of the Licensed Product.

9.3.4 The party being sued shall have the right to negotiate an appropriate licence from such third party and shall keep the other party fully informed as to progress of such negotiations. The party negotiating such licence shall use its reasonable efforts to minimise the amount of licence fees and royalties payable in respect of any such licence.

9.3.5 50% of any licence fees or royalties paid by Janssen under any licence negotiated pursuant to Clause 9.3.4 above shall be creditable against royalties due to Synaptech under this Agreement in respect of the countries covered by such third party rights only. Provided that in no event shall the royalties payable under Clause 5 be reduced under the provisions of this Clause 9.3.5 by more than 50%.

9.3.6 If Janssen decides to defend a suit or claim referred to in Clause 9.3.1 above then Janssen shall have the right to apply up to 50% of each Quarter's royalties otherwise payable to Synaptech under Clause 5 in respect of countries covered by such third party rights on sales of the allegedly infringing Licensed Products against its reasonable out of pocket expenses.

9.3.7 For the avoidance of doubt Clauses 9.3.5 and 9.3.6 shall only apply in respect of claims that the use and/or sale of Galanthamine for the treatment of Alzheimer's disease and/or related dementias infringes the right of a third party and shall not apply to any allegation or claim relating to the manufacture, production or formulation of the Licensed Product and/or delivery methods for the Licensed Product.

9.4 Compulsory Licences

In the event that in a country of the Janssen Territory which compels a compulsory license to be granted, and in the event such a compulsory license is granted in respect of the Patent, then subject to Clause 7.3 the parties shall share any royalty payment or payments payable under such granted compulsory license as to one third Synaptech and two thirds to Janssen

10. REPORTING; DATA AND IMPROVEMENT

Reporting

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10.1 Janssen will keep Synaptech informed each Quarter on the status of the development of Licensed Product by way of summary reports sent to Synaptech for its consideration. Ownership of such reports and any underlying data will at all times be retained by Janssen. Synaptech will treat such reports as confidential and in accordance with the confidentiality and non-use obligations of Clause 11, except that it may disclose such reports to a prospective licensee under its patent or patent applications for the use of Galanthamine in Japan under confidentiality undertakings similar to those provided for in Clause 11. If Synaptech appoints a licensee in Japan and the licensee wishes to use the data upon which the reports are based, Janssen and Synaptech will in good faith negotiate a reasonable compensation to be paid by Synaptech to Janssen for the disclosure to and use by Synaptech's licensee of such reports and such data.

10.2 It will be Janssen's responsibility to comply with any Adverse Drug Experience (ADE) reporting requirements in the Janssen Territory. Whenever any such ADE reports would require an amendment of the Product Approval in any given country of the Janssen Territory, Janssen will inform Synaptech of such amendment. It is however understood that Janssen will at any time during the term of this Agreement have the sole and discretionary right to decide on any issue directly or indirectly relating to any Product Approval or any application or amendment thereof. Similarly, whenever Janssen so informs Synaptech or elects to consult with Synaptech, such information or consultation shall in no event prevent, hinder or delay Janssen's reporting obligations towards regulatory authorities in any country of Janssen Territory.

Any information disclosed by Janssen to Synaptech pursuant to the provisions of this Clause 10.2 shall be treated by Synaptech as Confidential Information in accordance with the provisions of Clause 11. Synaptech in that respect further recognises that any such disclosure may seriously jeopardise any Product Approval in the Janssen Territory and hence Janssen's unfettered enjoyment of the rights granted hereunder.

In the event that Synaptech appoints a licensee under its patent or patent applications for the use of Galanthamine in the treatment of Alzheimer's disease and related dementias in Japan, parties will discuss and agree on a procedure for the exchange of any ADE's Janssen and such licensee both are required to disclose to the regulatory authorities in their respective territories and which ADE occurred with a Licensed Product of the other party in their respective territories.

10.3 Synaptech will have a non-exclusive and royalty free license for the Janssen Territory in respect of any Improvement developed by Janssen during the term of this Agreement. Janssen will have a non-exclusive and royalty free license for the Janssen Territory in respect of any Improvement developed by Synaptech during the term of this Agreement.

11. CONFIDENTIALITY

11.1 Synaptech and Janssen undertake to each other to keep (and shall procure that their respective employees (including employees of any Affiliate) shall keep) confidential all information supplied to each other during or in anticipation of this Agreement however

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obtained and in whatever form (the "Confidential Information") provided that Confidential Information shall not include the following:-

11.1.1 information which at the time of disclosure by one party to the other is in the public domain;

11.1.2 information which after disclosure by one party to the other becomes part of the public domain by publication except by breach of this Agreement;

11.1.3 information which the receiving party can establish by competent proof was already in its possession at the time of its receipt and was not acquired directly or indirectly from the other party; and

11.1.4 information received from third parties who are lawfully entitled to disclose such information.

11.2 Any Confidential Information received from the other party shall not be used for any purpose other than as provided or anticipated under this Agreement.

11.3 The confidentiality obligations contained in this Agreement shall continue for the duration of this Agreement and for a period of ten (10) years after termination or expiry of this Agreement.

11.4 The above provisions shall in no event prevent Janssen from disclosing any such data to regulatory authorities or other governmental agencies in support of any application for regulatory approvals or any amendments thereof or in general whenever required to disclose such information under any applicable law or regulation.

12. INDEMNITY

12.1 Except for those matters covered by Clause 9, in respect of which this Clause 12.1 shall not apply, Janssen shall assume all risks associated with the importation, manufacture, use, keeping, offer for sale or supply, sale or supply by, through or on behalf of Janssen or its Affiliates of Licensed Product (and related materials) for the Janssen Territory including, without limitation, claims based on product liability laws.

12.2 Without limit of time Janssen shall defend, indemnify and hold harmless Synaptech, Dr Bonnie Davis, a Permitted Transferee to whom rights under this Synaptech Agreement have been transferred, Dr. Bonnie Davis' estate and Synaptech's Affiliate Intelligen Corporation, and the latter only to the extent that it was holding the Ciba Data and the Patent in the United States of America from and against any and all claims, demands, losses, damages and expenses, including reasonable attorney's fees including but not limited to death, personal injury, illness, property damage or product liability arising from or in connection with any use or sale by Janssen, its Affiliates or sublicensees of Galanthamine throughout the world except to the extent that any such claims, demands, losses, damages and expenses, including reasonable attorney's fees, are due to the gross negligence or malpractice of Synaptech, Intelligen Corporation, Dr Bonnie Davis or a Permitted Transferee to whom rights under this Agreement have been transferred. In no event shall Synaptech, Intelligen Corporation, Dr Bonnie Davis or a

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Permitted Transferee be entitled to payment under this Clause 12.2 if it has already obtained payment under clause 12.2 of the Shire-Janssen Sub-Licence Agreement for the same claim, demand, loss, damage and expense.

12.3 To ensure that it can meet its obligations under this Clause 12 Janssen shall have its own insurance cover or be self-insuring.

13. SYNAPTECH KNOW-HOW

The use and disclosure of Synaptech Know-how and the exercise of Janssen's rights under this Agreement shall be subject to the export, assets and financial control regulations of the United States of America, including but without limitation, restrictions under regulations of the United States that may be applicable to direct or indirect re-exportation of Synaptech Know-how or equipment, products or services directly produced by use of Synaptech Know-how.

14. WARRANTIES

14.1 Synaptech warrants that it is the sole beneficial owner of the Patent and has the authority to grant the rights conferred in this Agreement.

14.2 Synaptech warrants that it has and throughout the term of this Agreement will have full access to the Synaptech Know-how of Dr Bonnie Davis c/o Schwartz & Salomon, 42nd Floor, 225 Broadway, New York NY 10007-3001 and that it is free to convey this Synaptech Know-how to Janssen.

14.3 Synaptech warrants that:

14.3.1 the Patent is subsisting and so far as Synaptech and Dr Bonnie Davis are aware is valid and enforceable, does not infringe the claims of any patent now owned or controlled by Synaptech or any Affiliate and does not come within the scope of the claims of any other pending patent application owned or controlled by Synaptech or any Affiliate or a predecessor in title of Synaptech; and

14.3.2 the Patent is the only patent or patent application in the Janssen Territory relating to Galanthamine for use in the treatment of Alzheimer's disease and related dementias in the possession or control of Synaptech, Dr Bonnie Davis or any Affiliate.

14.4 Synaptech warrants that it is entitled to grant the licence set out in Clause 2.3 and so far as it is aware the Cibs Data is accurate and complete.

14.5 Synaptech makes no warranties whatsoever, either express or implied, as to any matter including the merchantability or fitness of the Licensed Product for a particular purpose.

15. DURATION

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This Agreement and the licences granted under Clause 2 shall come into force on the date of this Agreement and unless terminated earlier in accordance with the provisions of this Agreement, this Agreement shall expire upon cessation of the obligation to pay royalties under Clause 5 and thereafter Janssen shall have a fully paid up royalty free licence.

16. TERMINATION

16.1 Termination by Either Party

This Agreement may be terminated by a party to this Agreement:-

16.1.1 Material Breach

Forthwith by notice in writing given at any time if the other party is in material breach of any of its obligations hereunder and the breach has not been remedied within 45 days of the defaulting party receiving notice specifying the breach and requiring its remedy. A material breach of this Agreement is a wilful act or omission by the breaching party that would deprive the injured party of a major part of the value of what it had contracted for and for which damages are not an adequate remedy. Any dispute over what constitutes a material breach of this Agreement shall be referred for resolution pursuant to Clause 19.11.

16.1.2 Insolvency

16.1.2.1 Forthwith by notice in writing given at any time if an order is made or a resolution is passed for the winding up of the other party (other than voluntarily for the purpose of solvent amalgamation or reconstruction) or an order is made for the appointment of an administrator to manage the other party's affairs, business and property or if a receiver (which expression shall include an administrative receiver) is appointed of any of the other party's assets or undertaking or if circumstances arise which entitle the court or a creditor to appoint a receiver or manager or which entitle the court to make a winding-up order or if a voluntary arrangement is proposed in respect of the other party or if the other party takes or suffers any similar or analogous action in consequence of debt.

16.1.2.2 All rights and licenses granted under or pursuant to this Agreement by Synaptech to Janssen are, and shall otherwise be deemed to be, for purposes of Section 365 (n) of Title 11, US code (the "Bankruptcy Code") licenses of rights to "intellectual property" as defined under section 101 (60) of the Bankruptcy Code. The parties agree that Janssen, as a licensee of such rights under this Agreement, shall retain and may fully exercise all of its rights and elections under the Bankruptcy Code. Synaptech

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agrees during the term of this Agreement to maintain current copies or detailed descriptions of all such intellectual property.

16.2 Termination by Synaptech

This Agreement and the licences granted in Clause 2 may be terminated by Synaptech:-

16.2.1 Non-Payment

If Janssen fails to pay any royalties or other payments due under this Agreement within 45 days of the due date this shall constitute a material breach of this Agreement and after receipt of notice of default shall be subject to the provisions of Clause 16.1.1

16.2.2 Challenge to the Patent

Forthwith by notice in writing given at any time if at any time Janssen disputes or directly or indirectly assists any third party to dispute the validity or enforceability of the Patent or any of the claims thereof.

16.2.3 Diligence

Synaptech may terminate this Agreement if Janssen fails to live up to its diligence obligations as provided for under Clauses 8.1 and 8.2 and after having been notified thereof by Synaptech fails to address the situation in accordance with Clause 16.1.1 provided that whenever such failure relates to a Major Country the rights shall be terminated only for such Major Country where Synaptech can demonstrate that Janssen failed to live up to its diligence obligations.

16.3 Termination by Janssen

16.3.1 Janssen may terminate this Agreement without cause by giving Synaptech 90 days written notice of termination.

16.3.2 Termination by Janssen pursuant to Clause 16.3.1 shall not give rise to any claim for compensation because of such termination.

17. CONSEQUENCES OF TERMINATION

17.1 Subject to Clauses 17.3, 17.4 and 16.1.2.2, on termination of this Agreement for any reason:-

17.1.1 Licences Terminated

The licences granted under Clause 2 shall terminate automatically and Janssen shall and shall procure that its Affiliates shall immediately stop all activities licensed hereunder except that Janssen and its Affiliates shall be permitted following termination to offer for sale and sell and supply

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remaining stocks of Licensed Product in their possession at the date of termination as quickly as reasonably possible and complete deliveries on contracts in force at that date subject to the payment of royalties under in accordance with the provisions of Clause 5.

17.1.2 Payment Due

Janssen shall within 30 days of the date of termination make all outstanding payments due to Synaptech, and subject to Clause 17.1 make a further payment of royalties due in respect of sales of Licensed Product thereunder.

17.1.3 Continuing Provisions

The following provisions of this Agreement shall continue in full force and effect: Clauses 1, 11, 12, 17, 19.7, 19.8, 19.11.

17.1.4 Return of Synaptech Know-how

Janssen shall return all Synaptech Know-how or copies thereof in its possession (or the possession of its Affiliates) to Synaptech.

17.1.5 Rights and Remedies for Breach

Any rights or remedies of either party arising from any breach of this Agreement shall continue to be enforceable.

17.2 In the event of termination by Synaptech for cause pursuant to Clause 16.2 or by Janssen pursuant to Clause 16.3:

17.2.1 Transfer of Trade Marks

Janssen shall free of charge promptly execute assignments in the form reasonably requested by Synaptech transferring to Synaptech or its designated Affiliates any trade marks and registrations or applications therefor used by Janssen in connection with the Licensed Products together with all goodwill associated with such trade marks

17.2.2 Use of Data, Studies and Product Approvals

17.2.2.1 Janssen shall free of charge promptly provide to Synaptech or its designated Affiliates all data, reports and other information arising out of or in connection with the development work conducted by or on behalf of Janssen or its Affiliates pursuant to this Agreement;

17.2.2.2 Janssen shall promptly provide to Synaptech or its designated Affiliates all Product Approvals and any applications therefor made or granted pursuant to this Agreement; and

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17.2.2.3 Synaptech shall be entitled to use in the Janssen Territory all information, know-how and data generated by or on behalf of Janssen in relation to the Licensed Product pursuant to this Agreement excluding any such information, Know-how or data related to the manufacturing of Galanthamine. Janssen shall not use such information, know-how or data for any purpose in the Janssen Territory or disclose it to any third party.

17.3 Whenever Synaptech terminates on a country by country basis pursuant to Clause 16.2.3 the provisions of Clauses 17.1 and 17.2 will only apply with respect to those countries where Janssen's rights are terminated.

17.4 In the event that this Agreement is terminated by Janssen for a material breach of Synaptech pursuant to Clause 16.1.1 then from and after the date of such termination Janssen shall be entitled to use Synaptech Know-how and shall be granted an irrevocable, exclusive license to use the Synaptech Know-how, the Ciba Data (subject to Clauses 4.5 - 4.8) and under the Patent to develop, use, make, have made and sell Licensed Product in the Janssen Territory. Janssen's sole consideration for such license will consist in the payment of 50% of the royalties otherwise due as stated in Clause 5.1.7 and Janssen will pay and report such royalties and the related Net Sales Value in accordance with the provisions of Clause 7.

18. FORCE MAJEURE

18.1 Neither party shall terminate this Agreement or be liable to the other under this Agreement for loss or damages attributable to any act of God, earthquake, flood, fire, explosion, strike, lockout, labour dispute, casualty or accident, war, revolution, civil commotion, act of public enemies, blockage or embargo, injunction, law, order, proclamation, regulation, ordinance, demand or requirement of any government or subdivision, authority (including, without limitation, regulatory authorities) or representatives of any such government, or any other cause beyond the reasonable control of such party, if the party affected shall give prompt notice of any such cause to the other party. The party giving such notice shall thereupon be excused from such of its obligations hereunder as it is so disabled during, but not longer than the existence of such cause.

18.2 If such cause continues unabated for a period of at least 90 days, both parties will meet to discuss what, if any, modifications should result from such Force Majeure.

19. MISCELLANEOUS

19.1 Performance by Affiliates

Synaptech recognises that Janssen may perform some of its rights and obligations through Affiliates, provided however, that Janssen shall remain solely responsible and be guarantor of the performance by its Affiliates and shall cause its Affiliates to comply with the provisions of this Agreement in connection with such performance.

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19.2 Severance

If any provision of this Agreement is held to be invalid or inapplicable by a court of competent jurisdiction the remaining provisions will continue in full force and the parties will make such amendments to this Agreement by the addition or deletion of wording as appropriate to remove the invalid or unenforceable part of such provision but otherwise retain the provision to the maximum extent permissible.

19.3 Waiver

Failure or delay by either party in exercising or enforcing any right or remedy under this Agreement in whole or in part shall not be deemed a waiver thereof or prevent the subsequent exercise of that or any other rights or remedy.

19.4 Headings

The headings in this Agreement are for convenience only and shall not affect its interpretation.

19.5 Assignment

Neither Synaptech nor Janssen shall assign, transfer, sub-licence, sub-contract, mortgage, charge or otherwise make over to any third party any of its rights or obligations under this Agreement without the prior written consent of the other party, except that Synaptech may assign its entire rights and obligations under this Agreement to the Permitted Transferee, provided that the Patent and the Synaptech Know-how are also assigned or otherwise transferred together with this Agreement. Prior to such assignment the Permitted Transferee shall covenant directly with Janssen to comply with the rights and obligations under this Agreement.

19.6 No Agency

Neither party shall act or describe itself as the agent of the other nor shall it make, or represent that it has authority to make, any commitments on the other's behalf.

19.7 Notices

19.7.1 Any notice or other document given under this Agreement shall be in writing in the English language and shall be given by hand or sent by prepaid airmail or by facsimile transmission to the address of the receiving party as set out in Clauses 19.7.3 and 19.7.4 below unless a different address or facsimile number has been notified to the other in writing for this purpose. A copy of any such notice shall be sent by either Synaptech or Janssen to Shire Holdings Limited at 22 Church Street, Hamilton HM11, Bermuda, Facsimile no: 1 809 292 2437.

19.7.2 Each such notice or document shall:-

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19.7.2.1 if sent by hand, be deemed to have been given when delivered at the relevant address;

19.7.2.2 if sent by prepaid airmail, be deemed to have been given 3 days after posting; and

19.7.2.3 if sent by facsimile transmission, be deemed to have been given when transmitted provided that a confirmatory copy of such facsimile transmission shall have been sent by prepaid airmail within 24 hours of such transmission.

19.7.3 Synaptech's address for service of notices and other documents shall be:-

For the attention of:
The Directors
Synaptech Inc
c/o Schwartz & Salomon
42nd Floor
225 Broadway
New York 10007-3001
USA

Facsimile No: 1 212 608 3785

19.7.4 Janssen's address for service of notices and other documents shall be:-

For the attention of:
I.V.P. Business Development
Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Facsimile No: 32 14 60 50 25

19.8 Law and Jurisdiction

This Agreement is made under the law of the State of New York excluding its conflict of law rules and subject to Clause 19.11.

19.9 Entire Agreement

19.9.1 This Agreement constitutes the entire agreement and understanding of the parties relating to the subject matter of this Agreement and supersedes all prior oral or written agreements, understandings or arrangements between them relating to such subject other than the side letter of even date between Synaptech, Janssen and Shire.

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19.9.2 The parties acknowledge that they are not relying on any agreement, understanding, arrangement, warranty, representation or term which is not set out in this Agreement.

19.9.3 No change may be made to this Agreement except in writing signed by duly authorised representatives of both parties.

19.9.4 The parties irrevocably and unconditionally waive any rights and/or remedies they may have (including without limitation the right to claim damages and/or to rescind this Agreement) in respect of any misrepresentation other than a misrepresentation which is contained in this Agreement.

19.9.5 Nothing in this Clause 19.9 shall operate to:

19.9.5.1 exclude any provision implied into this Agreement by law and which may not be excluded by law; or

19.9.5.2 limit or exclude any liability, right or remedy to a greater extent than is permissible under law.

19.10 Compliance with Local Requirements

If in any jurisdiction the effect of any provision(s) of this Agreement or the absence from this Agreement of any provision(s) would be to prejudice the Patent or any remedy under the Patent, the parties will make such amendments to this Agreement and execute such further agreements and documents limited to that part of the Janssen Territory which falls under such jurisdiction as may be necessary to remove such prejudicial effects.

19.11 Disputes

If any dispute arises out of or in relation to this Agreement, the parties will endeavour to settle such dispute amicably between themselves. In the event that the parties fail to agree, any such dispute shall be finally settled by arbitration administered by and according to the Rules of Commercial Arbitration of the American Arbitration Association. The arbitration shall take place in New York, New York State. The arbitration panel shall consist of one (1) arbitrator and the decision shall be final and binding on the parties and their legal successors. The Arbitrator may, at his discretion, provide for discovery by the parties not to exceed four (4) months from the date of filing of the notice of arbitration and the arbitrator shall render his decision within thirty (30) days of the completion of the hearing and may, at his discretion award costs and expenses but shall not award punitive damages.

19.12 Publicity

In the absence of specific agreement between the parties, neither party shall originate any publicity, news release or public announcement, written or oral, whether to the public or press, relating to this Agreement including its existence, the subject matter to which it relates, performance under it or any of its terms, to any amendment hereto

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save only such announcements as in the opinion of counsel for the party making such announcement is required by law to be made. Any such announcements shall be factual and as brief as possible. If a party decides to make an announcement required by law, it will give the other party notice as soon as possible but, where possible, not less than fifteen (15) days advance written notice of the text of the announcement so that the other party will have an opportunity to comment upon the announcement.

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ADDENDUM I

made this 29 day of June, 1999 ("Effective Date") to the License Agreement executed November 30, 1995 (hereinafter "License Agreement") by and between

SYNAPTECH INC. a company organised and existing under the laws of the State of New York whose principal place of business is c/o Schwartz & Salomon, 42nd Floor, 225 Broadway, New York 10007-3001 U.S.A.
(hereinafter referred to as "SYNAPTECH")

and

JANSSEN PHARMACEUTICA N.V., a Belgian business corporation organized and existing under the laws of Belgium, with registered office at B-2340 Beerse, Belgium, Turnhoutseweg 30
(hereinafter referred to as "JANSSEN")

RECITALS

WHEREAS, SYNAPTECH is the beneficial owner of the rights, title and interest of the Patent in Japan; and

WHEREAS, SYNPATECH is willing to grant to JANSSEN, and JANSSEN is willing to accept, an exclusive license under the Patent and the SYNAPTECH Know-How to develop, make, have made, keep, use, market and/or sell the Licensed Product in Japan; and

WHEREAS, SYNAPTECH and JANSSEN agree to supplement and amend the License Agreement in order to vest in JANSSEN such exclusive rights in Japan in accordance with the License Agreement and such additional terms and conditions as set forth hereinafter.

NOW, THEREFORE it is agreed as follows :

1. DEFINITIONS

Unless clearly indicated otherwise, the capitilized terms used in this Addendum I shall have the meaning defined in Article 1 of the License Agreement.

1.1. The definition of "Licensed Territory" shall be amended to include also Japan.

1.2. The definition of "Major Country" shall be amended to include also Japan.

BD

1.3. For the purpose of this Addendum "Phase II Studies" shall refer to the initial clinical trials of Licensed Product on a limited number of patients for the purpose of determining, dose-ranging and evaluating safety and efficacy.

2. SIGNING FEE AND MILESTONE PAYMENTS

In consideration of the rights and licenses granted by SYNPATECH in relation to Japan and in addition to the payments referred to in Sections 3.1. and 3.2. of the License Agreement, JANSSEN shall pay to SYNAPTECH the following non-refundable amounts without any deduction whatsoever:

2.1. Promptly following the signature of this Addendum a signing fee of USD 2,500,000 (US Dollars);

2.2. Within thirty (30) days following commencement of Phase II Studies in Japan a milestone payment of USD 1,000,000 (US Dollars);

2.3. Within thirty (30) days following the submission of the application for Product Approval with the regulatory authorities in Japan a milestone payment of USD 750,000 (US Dollar); and

2.4. Within thirty (30) days following receipt of the Product Approval in Japan a milestone payment of USD 250,000 (US Dollar).

3. CIBA DATA

For the avoidance of doubt both parties agree that Section 4.6. of the License Agreement shall not apply to any use of the Ciba Data by JANSSEN or a Sublicensee in Japan.

4. ROYALTY

In consideration for the rights and licenses granted in relation to Japan, JANSSEN agrees to make to SYNAPTECH royalty payments in accordance with the provisions of Article 5, it being understood that the Patent and Know-How Royalty Rate, the Know-How Royalty Rate and the Reduced Know-How Royalty Rate with respect to the Net Sales Value in Japan shall be 7%, 5% and 3% respectively.

5. COMMERCIALISATION

The provisions of Article 8 shall apply with respect to the development and commercialization of Licensed Product in Japan.
Notwithstanding the above the parties agree that the timelines set forth in Schedule 2 of the License Agreement and referred to in Article 8 shall be supplemented as follows with respect to Japan.

Depending whether or not international phase III clinical studies can be used in support of the application for Product Approval in Japan, the submission date in Japan is 2006 (if international phase III clinical studies can be used) or 2008 (if international phase III clinical studies can not be used) .
In connection with Section 8.2.2. and taking into account the competitive market position in connection with second generation cholinesterase inhibitors, JANSSEN agrees to provide for an appropriate sales force coverage of the target audience in Japan in order to comply with its reasonable effort commitment as set forth in said Section 8.2.2. either completely via its own sales force or with the help of one or more Sublicensee's sales forces.

6. TERMINATION AND EFFECTS OF TERMINATION

The provisions of Article 16 and 17 shall apply with respect to Japan, except that in case of termination for cause by SYNATPECH pursuant to Section 16.2 or by JANSSEN pursuant Section 16.3., the Product Approval and related Trademark with respect to Japan shall not automatically be transferred to SYNAPTECH and the provisions of Section 17.2. and 17.3 shall not apply.
In such instance SYNAPTECH, JANSSEN and Shire shall in good faith and as expeditiously as possible agree on a course of action in accordance with the provisions of relevant preexisting agreements relating to the respective proprietary rights of all the parties. In case the parties can not come to an agreement within a period of ninety (90) days, such matter may be submitted to three party arbitration in accordance with Section 19.11 of the License Agreement and Section 26 of the Shire-Synaptech Agreement. Both parties acknowledge that both SYNAPTECH and Shire shall in any event be entitled to (i) utilize the Know How and the development data generated in connection with the use of galantamine and (ii) refer to the Product Approval in Japan free of charge, provided always that any such use of the Know-How and data and referral rights of SYNAPTECH and Shire shall be restricted to the indications covered by the patents owned or controlled by SYNAPTECH and Shire respectively.

WITNESS the signature of both parties by their duly authorized officers.

JANSSEN PHARMACEUTICA N.V.
This 29th day of June 1999

G. Vercauteren
International Vice President
Business Development

G. Van Reet
Managing Director

SYNAPTECH INC.
This 30th day of May 1999
July

Scientific Director
(title)

By Bonnie Hall
(title)

July 30, 1999
Witness Judith Wenzin

FV/ch/99.F.29

TO: Chatel Herman
Secretary to Filip Verhoeven

This is to confirm that I have signed the addendum to the basic agreement between Synaptech and Janssen so as to extend it to Japan so that the signing fee of $2,500,000 is now due.

Bonnie Davis, M.D.

July 30, 1999

GENERAL MANAGEMENT **APPROPRIATION REQUEST**

March 2, 1999

To
E.D. Strobino
to
W.C. Weldon
to
Pharmaceuticals Group
to
R.J. Darretta
to
Executive Committee

From: Staf Van Reet
Valentino Tanca

Cc:

Alan Dunton	Hiroshi Kojima	Ajit Shetty
Bruce Goodwin	Jos Laurijssen	Leo Van Ginckel
Thad Huston	Wim Parys	Herman Van Hoof
Rene Hex	Ko Sekiguchi	Filip Verhoeven

SUBJECT : APPROPRIATION REQUEST TO ADD JAPAN TO THE LICENSED TERRITORY FOR GALANTAMINE (CONTRACT WITH SHIRE AND SYNAPTEC)

Executive summary

Your approval is requested to sign an addendum to the agreement with Shire and Synaptec to add Japan to the licensed territory for galantamine.

Synaptec is the patent holder of the galantamine medical use patent for Alzheimer's disease (AD) and Shire holds certain rights for the use of galantamine in AD and has the rights to the galantamine medical use patent for Chronic Fatigue Symptom (CFS).

Japan is already included in the worldwide agreement for the use of galantamine in Obstructive Sleep Apnoea (OSA). This agreement was very recently signed with A* Science Invest AB.

Japan was not included in the original agreement covering AD and CFS because of uncertainties related to the availability of synthetic galantamine (development of extracted product is difficult in Japan) and because of the competitive situation of Alzheimer products in Japan. Today the availability of synthetic material is a fact and the development of several AD products in Japan has been delayed or discontinued. This has substantially improved the outlook for galantamine in Japan.

The total amount of license fee and milestones which Janssen will have to pay to Synaptec and Shire to obtain galantamine rights for Japan will be 7.1 mio USD, of which 4.5 mio USD is for AD to Synaptec and 2.6 mio USD for CFS to Shire (see details further on). At the time of signing we will have to pay 2.5 mio USD to Synaptec and 0.5 mio USD to Shire.

Based on the new regulations for clinical development in Japan it is likely that only Phase I and II clinical trials will have to be repeated in Japan and that international Phase III data can be used. Only if phase I and II data differ from international data we will have to do a Japanese phase III study.

In the first scenario, introduction of galantamine for Alzheimer's disease is planned in 2006 and in case a phase III study will have to be done locally introduction will be in 2008. These introduction dates are conservative and it is the objective to move these dates forward with 1-2 years.

Financial projections of this base case scenario show peak sales of 97.6 mio USD in 2013. The IRR is 29 % and the NPV amounts to 20.9 mio USD.

In case phase I and II clinical data are different from the international data, a phase III clinical trial may be required. Under that scenario the introduction will be postponed until 2008. The financial data are as follows : peak sales of 82.8 mio USD in 2014, an IRR of 21 % and an NPV of 9.1 mio USD.

R&D expenses up to file submission are 13.4 mio USD (including 20 % contingency) in the first scenario and 17.4 mio USD when a phase III clinical study needs to be done in Japan. After registration another 2.0 mio USD is foreseen for post marketing surveillance. Large phase IV studies are not conducted in Japan.

Important to note is also that the indications of CFS and OSA have been considered as upside potential and sales, development expenses and most milestones for CFS have not been included in the projections. However the 0.5 mio USD signing fee for CFS has been included.

Market background and competition

During the last two decades patients with symptoms of Alzheimer's disease were traditionally treated in Japan with nootropics. However the Japanese government has withdrawn most of these products during recent years because of lack of efficacy.

Several acetylcholinesterase inhibitors are in development in Japan for Alzheimer's disease. The most advanced compound is donepezil (Eisai), which is expected to obtain registration before the end of this year. Rivastigmine from Novartis is expected to reach the market in 2001.

There are at least 3 other cholinesterase inhibitors in clinical development : amiridin (Nikken), TAK-147 (Takeda) and metrifonate (Bayer). However all these compounds have encountered problems during their development and it is uncertain whether any of them will reach the marketplace.

In the forecast assumptions for galantamine it has nevertheless been assumed that all these products will be introduced ahead of galantamine. Galantamine will reach a peak market share within this group of cholinesterase inhibitors of 18 %.

A net selling price of 3.5 USD per day has been assumed. This price is equivalent to the price of donepezil in the USA and it is also the price which Eisai is seeking for donepezil in Japan.

Rationale for decision to include Japan in the licensing territory

When the original contract was signed with Shire and Synaptec in 1995, Japan was not part of the license because :

- the number of cholinesterase inhibitors in development in Japan was larger than in other countries. Several Japanese products which were not found in other countries were in the list and these Japanese products were in a rather advanced stage of development. However since that time most of these products have encountered difficulties in their development and it is now expected that only donepezil and rivastigmine will be well ahead of galantamine.
- synthetic galantamine was not available at that time and it was still uncertain how successful the process development of a synthesis method would be. In Japan a development of galantamine initially based on extracted material has been excluded from the beginning because development of such natural products is difficult.
- AD was still very much under diagnosed in Japan. Development of cholinesterase inhibitors have gradually changed this picture.

In addition to these elements, the positive international phase III results and the strategic fit of galantamine with risperidone have contributed to the decision of Janssen-Kyowa to express an interest in galantamine.

Also the fact that virtually the whole non-clinical file is already internationally available and that most likely the international phase III clinical studies can be used have contributed to the decision.

Lastly the new indication of OSA adds further upside potential to galantamine.

Contractual conditions

Janssen has obtained an exclusive license from Shire and Synaptec for Japan.

For sales in Alzheimer's disease Janssen will pay an 8 % know how royalty to Shire and a 7 % patent royalty to the patent holder Synaptec. This compares with a total royalty rate of 17 % for Europe and 15 % for the USA.

For sales in CFS Janssen will pay 12 % royalty to Shire (of which 5 % will go to the CFS patent holder Dr. Snorrason).

Royalties for the indication of OSA will be the same as for other countries in the world (see recent agreement with A^+ Science).

The milestone schedule is as follows :

	Synaptec (AD)	Shire (CFS)
Signing fee	2.5 mio USD	0.5 mio USD
Successful completion phase II	1.0 mio USD	0.5 mio USD
Submission reg. File	0.75 mio USD	0.8 mio USD
Registration	0.25 mio USD	0.8 mio USD

As mentioned above the AD signing fee and milestones and the 0.5 mio USD CFS signing fee have been taken up in the financial projections.

These milestones are higher than the ones paid for other parts of the world because of the more advanced stage of development of the product and because of the very keen interest of at least one other Japanese company (Chugai).

Financial projections

Key financial data : see separate page

Assumptions : see separate page

P&L projections : see separate pages (2)

GALANTAMINE - JAPAN
Forecast Assumptions

Launch	2006 2Q (Downside Scenario of 2006 2Q Launch when PIII domestic trial is required)
Sales	available AD population base: 0.67% of the general population in Year 1 growing to 0.978% in Year 10 3.33% of the population over 65 years of age in Year 1 growing to 3.88% in Year 10 Number of patients diagnosed : 76 % in year 1 growing to 80 % in year 10 50 % of diagnosed patients will use a cholinesterase inhibitor Market share galantamine: 6% in year 1 growing to 18% in year 6 declining to 7% in year 10
Price	price per day same as Aricept target price in Japan (equivalent to US price): 500 yen (12 mg bid) 3.5 USD
COGS	average cost per tablet: 0.175 USD or 10% of NTS dosage: 2 tablets per day
Royalties	royalty to Synaptech of 7% of NTS royalty to Shire of 8% of NTS
Marketing	Forecast marketing expenses are in line with Janssen-Kyowa's historical figures Forecast selling expenses are in line with Janssen-Kyowa's projected allocation of selling efforts
R&D	total cost of 11.2 mio USD + 20% contingency (additional 3.3 mio USD + 20% contingency if Phase III domestic trial is required) post approval R&D: 2.0 mio USD (0.3%) of NTS (Unlike in the West, large scale Phase IV studies are not conducted)
Milestones	Alzheimer's disease to Synaptec: upon signing 2.5 mio USD end phase II 1.0 mio USD NDA filing 0.75 mio USD NDA approval 0.25 mio USD Chronic Fatigue Syndrome to Shire: upon signing 0.5 mio USD
Other Expenses	administration: 2.9% of NTS distribution: 3.0% of NTS effective tax rate: 47.6% days receivable: 90 days months inventory: 90 days discount rate: 14%

GALANTAMINE - JAPAN
KEY FINANCIAL DATA

	(Mio USD)			
	Peak Sales	R&D Investment	NPV	IRR
Launch 2006 - no Phase III required	97.6	13.4	20.9	29%
Launch 2008 - Phase III required	82.8	17.4	9.1	21%

Highly Confidential

Base Case - Launch 2006

GALANTAMINE - JAPAN
Financial Analysis : P&L and Cash Flow Highlights
(Dollars in Millions)

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	TOTAL
NET SALES (85% of market price)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$20.1	$38.9	$51.1	$65.0	$78.8	$92.0	$94.7	$97.6	$88.7	$79.2	$706.1
Sales Growth %		N/A	N/A	N/A	N/A	N/A	N/A	N/A	94%	32%	27%	21%	17%	3%	3%	-9%	-11%	
GROSS PROFIT	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$15.1	$29.2	$38.4	$48.7	$59.1	$69.0	$71.1	$73.2	$66.3	$59.4	$529.8
% to Sales	N/A	N/A	N/A	N/A	N/A	N/A	N/A	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%
OPERATING EXPENSES (EXCL. R&D)	$0.0	$0.0	$0.0	$0.0	$0.0	$3.3	$5.6	$21.1	$21.3	$19.6	$17.1	$14.6	$15.4	$18.5	$15.7	$15.2	$14.6	$177.1
% to Sales	N/A	N/A	N/A	N/A	N/A	N/A	N/A	105%	55%	38%	26%	19%	17%	19%	16%	17%	18%	25%
R&D	$1.4	$1.6	$1.7	$2.4	$2.5	$2.4	$1.1	$0.4	$0.4	$0.7	$0.2	$0.1	$0.1	$0.2	$0.4	$0.0	$0.0	$15.5
% to Sales	N/A	N/A	N/A	N/A	N/A	N/A	N/A	2%	1%	1%	0%	0%	0%	0%	0%	0%	0%	2%
LICENSING RELATED EXPENSES	$1.0	$1.5	$0.5	$0.5	$0.5	$0.8	$0.0	$0.3	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.8	$0.0	$0.0	$5.8
INCOME BEFORE TAXES	($1.4)	($1.6)	($1.7)	($2.4)	($2.6)	($5.7)	($4.8)	($6.4)	$7.4	$18.1	$31.6	$44.4	$53.5	$53.3	$57.5	$52.3	$44.8	$337.0
NET INCOME	($1.3)	($1.6)	($1.1)	($1.5)	($1.6)	($3.4)	($2.9)	($3.5)	$3.9	$9.5	$16.5	$23.3	$28.0	$29.0	$30.1	$26.9	$23.5	$174.0
% to Sales	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-17%	10%	19%	25%	30%	30%	31%	31%	30%	30%	25%
CASH FLOW	($3.2)	($1.2)	($0.5)	($0.9)	($1.1)	($3.0)	($2.6)	($4.6)	$0.9	$7.3	$13.9	$20.7	$26.6	$28.6	$29.6	$28.2	$24.9	$163.1
CUMULATIVE CASH FLOW	($3.2)	($4.4)	($4.9)	($5.8)	($6.9)	($9.9)	($12.5)	($17.0)	($16.1)	($8.8)	$5.1	$25.0	$51.8	$80.3	$110.0	$136.2	$163.1	

Results	10 Years	Corp Value
Discount Rate	14.0%	14.0%
NPV	$20.9	$28.6
IRR	29%	31%

GALANTAMINE - JAPAN - DOWNSIDE SCENARIO - DELAY OF LAUNCH
Financial Analysis : P&L and Cash Flow Highlights
(Dollars in Millions)

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	TOTAL
NET SALES (80% of market price)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$14.0	$35.0	$47.5	$59.5	$72.5	$74.6	$82.8	$73.1	$68.4	$63.4	$590.4
Sales Growth %		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	151%	35%	25%	22%	3%	11%	-12%	-7%	-7%	
GROSS PROFIT	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$10.5	$26.2	$35.5	$44.6	$54.3	$56.0	$62.1	$54.8	$51.3	$47.5	$442.8
% to Sales	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%
OPERATING EXPENSES (EXCL. R&D)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$2.9	$3.3	$20.4	$20.7	$18.9	$16.3	$13.8	$13.9	$14.4	$13.8	$13.6	$13.3	$168.4
% to Sales	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	146%	59%	40%	27%	19%	19%	17%	19%	20%	21%	29%
R&D	$1.4	$1.9	$1.9	$2.2	$2.3	$2.5	$2.6	$2.0	$0.3	$0.4	$0.4	$0.7	$0.2	$0.1	$0.1	$0.2	$0.0	$0.0	$0.0	$19.4
% to Sales	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	3%	1%	1%	0%	0%	0%	0%	0%	0%	0%	3%
LICENSING RELATED EXPENSES	$1.0	$1.5	$0.5	$0.3	$0.5	$0.0	$0.0	$0.0	$0.0	$0.3	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$5.0
INCOME BEFORE TAXES	($1.4)	($1.9)	($1.9)	($2.2)	($2.3)	($2.5)	($2.6)	($4.9)	($3.6)	($10.6)	$5.1	$15.8	$28.1	$40.4	$41.9	$47.4	$41.0	$37.7	$34.2	$250.0
NET INCOME	($1.3)	($1.6)	($1.2)	($1.4)	($1.5)	($1.3)	($1.4)	($3.0)	($1.9)	($5.5)	$2.7	$9.3	$14.7	$21.2	$22.0	$24.9	$21.8	$19.7	$17.9	$132.6
% to Sales	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-40%	8%	20%	25%	29%	29%	30%	29%	29%	28%	22%
CASH FLOW	($3.2)	($1.3)	($0.6)	($0.9)	($1.0)	($1.2)	($1.4)	($2.8)	($2.0)	($5.6)	($0.6)	$6.1	$12.3	$18.8	$21.4	$23.6	$22.9	$20.5	$18.7	$124.1
CUMULATIVE CASH FLOW	($3.2)	($4.5)	($5.1)	($6.0)	($6.9)	($8.2)	($9.5)	($12.3)	($14.3)	($19.8)	($20.4)	($14.3)	($2.0)	$16.8	$38.4	$62.1	$85.0	$105.4	$124.1	

Results	10 Years	Corp Value
Discount Rate	14.0%	14.0%
NPV	$9.1	$13.6
IRR	21%	23%

September 13, 1996

Dear Sirs,

Reference is made to :

(1) License Agreement dated 30th November 1995 between Synaptech Inc. ("Synaptech") and Shire Holdings Limited ("SHL") and Shire International Licensing BV ("SILBV") collectively ("the "Synaptech-Shire License Agreement") and

(2) Sub-license Agreement dated 30th November 1995 between Shire International Licensing BV and Janssen Pharmaceutica N.V (the "Shire-Janssen Sub-license Agreement)

(3) License Agreement dated 30th November 1995 between Synaptech Inc. and Janssen Pharmaceutica N.V. (the "Synaptech-Janssen License Agreement")

This letter is written to confirm the request of SHL, SILBV and Janssen pursuant to the Synaptech-Shire License Agreement, the Shire-Janssen Sub-license Agreement and the Synaptech-Janssen License Agreement that SHL, SILBV and Janssen require the Ciba Data.

It is thereby agreed that the definition of the Ciba Data shall be amended to include the data in the documents listed in the first schedule to this letter and that the aggregate amount to be paid by Janssen, Shire and SILBV under the agreements referred to above shall be increased by $200,000 (Two hundred thousand United States Dollars) to $2,000,000 (Two million United States Dollars).

It is hereby agreed that in Clause 14.1. (d) of the Synaptech-Shire License Agreement, Clause 14.4. of the Synaptech-Janssen License Agreement and Clause 14.1.4. of the Shire-Janssen Sub-license Agreement after the words "and so far as it is aware the Ciba Data is accurate and complete" there shall be inserted therefor the following "except in respect of that part of the Ciba Data listed in Schedule A to this letter".

It is hereby agreed that whenever the Synaptech-Janssen License Agreement is terminated by Synaptech pursuant to Clause 16.1. or 16.2. or by Janssen pursuant to Clause 16.3., Synaptech will be entitled to use the Ciba Data in the Janssen Territory for Alzheimer's disease and any other indication.

Whenever the Synaptech-Shire License Agreement is terminated by Synaptech pursuant to Clause 23.1 or 23.2, Synaptech will be entitled to use the Ciba Data in the Territory (as defined in the Synaptech-Shire License Agreement) for Alzheimer's disease and any other indication, provided the rights with respect to the Territory are not licensed directly to Janssen in accordance with the provisions of Clause 5 of a letter between Janssen-Shire and Synaptech dated November 30, 1995.

In the event of termination of the Synaptech-Janssen License Agreement and/or Synaptech-Shire License Agreement in accordance with the above-mentioned Clauses, Janssen and/or Shire - depending on the Agreement(s) actually terminated - will refrain from using the Ciba Data in connection with Alzheimer's disease and related dementia's.

It is however understood and agreed that notwithstanding any such termination of the Synaptech-Janssen License Agreement and/or Synaptech-Shire License Agreement, Janssen and Shire shall maintain the right to use the Ciba Data in the Janssen Territory and/or Territory in connection with indications other than Alzheimer's disease or related dementia's.

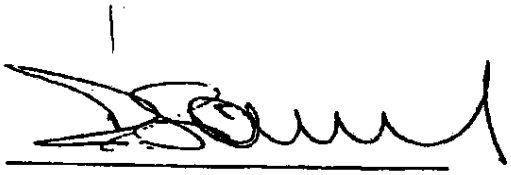
Notwithstanding the provisions of Clauses 3.4. of the Synaptech-Shire License Agreement and Clause 4.7. of the Synaptech-Janssen License Agreement, Janssen and Shire acknowledge that the documents listed in Schedule A to this letter pertaining to clinical studies only or the content thereof may have been or may be published by clinical investigators who participated in such studies and to the extent of such publication the aforementioned provisions shall not apply.

Janssen and Shire furthermore acknowledge that also Synaptech or Dr. Bonnie Davis may publish the said clinical data, it being understood that prior to any such publication Synaptech or Dr. Bonnie Davis shall seek the prior written consent of Janssen and Shire, such consent not to be unreasonably withheld.

It is further agreed that notwithstanding the terms of each of the agreements referred to above, payment of the $ 2,000,000 shall be made directly by Janssen on behalf of itself and Shire to Synaptech within five days of the signature by Synaptech of this letter, provided such signature by Synaptech shall coincide with the signature of Synaptech's Affiliate Intelligen of the Ciba-Geigy-Intelligen Agreement, transferring the exclusive rights to the Ciba Data to Intelligen.
Synaptech hereby acknowledges that payment by Janssen of this sum as aforesaid to Synaptech shall be deemed by Synaptech to be good discharge of the obligations of Janssen, Shire and SILBV under the respective Agreements relating to the acquisition of the Ciba Data.

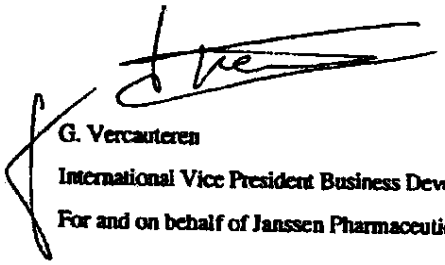
Synaptech furthermore confirms that the exclusive rights to the Ciba Data will be promptly assigned to it following the countersignature of the Intelligen-Ciba-Geigy Agreement by Ciba-Geigy. In the event the Intelligen-Ciba-Geigy Agreement would not be promptly countersigned by Ciba-Geigy following Intelligen's signature thereof, the above $ 2,000,000 will be refunded to Janssen upon Janssen's request to do so.

Yours faithfully,



For and on behalf of Shire Holdings Limited

For and on behalf of Shire International Licensing BV



G. Vercauteren
International Vice President Business Development
For and on behalf of Janssen Pharmaceutica N.V.

On behalf of Synaptech Inc. I accept the above terms and conditions

For and on behalf of Synaptech Inc.

22 Is 1997

SCHEDULE A

Toxicology Studies	MIN number
Dog 4-Week Pilot	911164
Rat 4-Week Pilot	911183
Rat Acute Pilot	911204
Dog Acute	911260
Rat 4-Week Pilot	911262
Rat 26/52-Week	921003
Dog 26/52 Week	911004
Ames Test	921238
Rat Acute	921245
Mouse Acute	921252
Mouse 13-Week Pilot	931142

Clinical Study

Protocol 01, "A Placebo-Controlled Double-Blind Enriched De-Challenge Efficacy, Safety and Tolerability Trial of Galantamine in Mild to Moderately Severe Primary Degenerative Dementia (Alzheimer Disease)"

SCHEDULE 1

Major Countries

USA

Canada

Mexico

The Republic of Korea

Taiwan

SCHEDULE 2

Product Approval Submission Timetable

COUNTRY	SUBMISSION DATE
USA	2002
Canada	2002
Mexico	2002
The Republic of Korea	2002
Taiwan	2002

11/30/95

Agreed by the duly authorised representatives of the parties the day year first above written:

For and on behalf of Synaptech Inc)
Signed)
Name:)
Title:)

For and on behalf of Janssen)
Pharmaceutica NV.)
Signed:)
Name: G. Van Reet
Title Managing Director

For and on behalf of Janssen)
Pharmaceutica NV.)
Signed:)
Name: A. Shetty
Title: Executive Vice President

Agreed by the duly authorised representatives of the parties the day year first above written:

For and on behalf of Synaptech Inc Signed Name: Title:	)	Bonnie M Davis MD Scientific Director
For and on behalf of Janssen Pharmaceutica NV. Signed: Name: Title:	)	
For and on behalf of Janssen Pharmaceutica NV. Signed: Name: Title:	)	

INTELLIGEN CORPORATION
P.O. BOX 357
COLD SPRING HARBOR, NEW YORK 11724
TELEPHONE (516) 423-3106
FAX (516) 423-3106

Nov 30 1995

This will confirm that US Patent # ~~45~~ 4663318 has been transferred to Synaptech Inc.

Bonnie Davis

Bonnie M Davis MD
Chief Executive Officer

EXHIBIT 15

Douglas G. Watson, President
Pharmaceuticals Division

Ciba-Geigy Corporation
556 Morris Avenue
Summit, NJ 07901-1398
Telephone 908 277 5200

November 10, 1993

CERTIFIED MAIL/RETURN RECEIPT REQUESTED

Intelligen Corporation
P.O. Box 157
Cold Spring Harbor, New York 11724

Attention: Dr. Bonnie Davis

Re: License Agreement by and between Ciba-Geigy Corporation ("Ciba") and Intelligen Corporation ("Intelligen"), dated September 28, 1990 ("Agreement")

Dear Dr. Davis:

Pursuant to Article 7.2 of the Agreement, this letter shall serve as notice to Intelligen by Ciba that Ciba exercises its right to terminate the Agreement effective thirty (30) days from the date hereof.

The rights and obligations of both Ciba and Intelligen upon the effective date of termination are set forth in said Article 7.2.

We appreciated having had the opportunity to study galanthamine under the Agreement.

Thank you for your attention to this matter.

Very truly yours,

D Watson

Douglas G. Watson

cc: John Richards, Esq.
(Certified Mail/
Return Receipt Requested)

EXHIBIT 16

MITSUI
PHARMACEUTICALS, INC.
● 12-2, Nihonbashi 3-chome Chuo-ku Tokyo 103 Japan ● (The 6th floor of Asahi Building)
● Telephone (Tokyo) 274-1711 ~ 5 ● Cable Mitsupharm Tokyo ● Telex 0222-3622(2223622 MTCrIBM)

Our Ref. No. 0017
February 3, 1989

Dr. Bonnie M. Davis
17 Seacrest Drive
Huntington
New York 11743
U. S. A.

Re: Galanthamine

Dear Dr. Davis,

I apologize you a long delay of our reply for the evaluation of the captioned compound. On your esteemed compound galanthamine our research groups for the evaluation of Alzheimer's disease area carefully studied the confidential information and the additional information presented to us on April 13 and November 2, 1988, respectively.

Though our research scientists are keeping a high interest in this compound from an academic point of view, our clinical development staffs emphasized that it is generally believed that regarding such sort of drugs there is quitely poor relation between animal data and clinical efficacy in patients with Alzheimer's disease and therefore, clinical studies of such drugs bring to us a difficulty of estimation of our reseach and development schedule and expense to proceed with the further development. Moreover, they are afraid that unexpected adverse effects may occur in patients during a long term treatment because of a similarity of its chemical structure to codein.

... Cont'd

Plaintiff's Exhibit
PX - 526

MITSUI
PHARMACEUTICALS, INC.

Our Ref. No. 0017

As a result, to be frank, we reached a negative conclusion to take up your compound and I regret my response could not be more favorable to you.

Enclosed are the confidential documents you provided and we greatly appreciate your kind cooperation in giving us an opportunity of studying your compound and sincerely hope to have another chance of collaboration with you in the future.

With best regards.

Sincerely yours,

MITSUI PHARMACEUTICALS, INC.

Takafumi Kitano Ph. D.
Manager
New Product Plannig Dept.

Encl.

c.c.: Mr. M. Hattori, Mitsui & Co., New York
Mr. K. Kataoka, Mitsui & Co., Tokyo

EXHIBIT 17

THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 49001, U S A
TELEPHONE (616) 323-4000

PHARMACEUTICAL RESEARCH
& DEVELOPMENT

NORMAN M POLLACK PH D
Contract Consultant
Research Contract Liaison

TELEPHONE (616) 385-7182
TELEX 910-240 1466
FACSIMILE (616) 385-7373

September 15, 1987

Bonnie M. Davis, M D.
17 Seacrest Drive
Huntington, NY 11743

Dear Dr. Davis:

Thank you for your letter of July 13 and the additional information on the use of galanthamine in an animal model. This information has been reviewed with interest by our CNS Research Unit, but I am afraid that it has not prompted a reversal of our earlier conclusion, primarily because we are already fully committed to other mechanistic approaches to Alzheimer's disease which we consider more promising than that offered by galanthamine.

We do appreciate your interest in working with Upjohn, and we wish you success in your effort to find an industrial sponsor.

Sincerely,

Norman M. Pollack, Ph.D.

ejw

Plaintiff's Exhibit
PX - 586

EXHIBIT 18

17 Seacrest Drive
Huntington, New York
516-423-3182
December 29, 1987

Dr. William Cressman
Assistant Vice President for Licensing and Business Development
Wyeth Ayerst Research
Wyeth Laboratories
P.O. Box 8299
Philadelphia, Pa. 19101

Dear Dr. Cressman:

Enclosed is a new set of materials on the use of galanthamine for Alzheimer's disease.

There are 1) a summary of relevant information, 2) a copy of the patent, and 3) four main categories of reprints: biochemistry of Alzheimer's disease, cholinergic treatments of Alzheimer's disease, pharmacologic properties of galanthamine, and toxicity information, such as is available.

The points that the materials will make are as follows:

Biochemistry of Alzheimer's Disease

Perry, Tomlinson, Blessed et al - The cholinergic deficit is present in all Alzheimer patients and correlates with the degree of dementia.

Cholinergic Treatments of Alzheimer's Disease

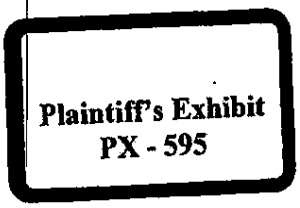
Thal, Fuld, Masur et al - Physostigmine-induced improvement in cognitive function in Alzheimer's disease correlates with the amount of cholinesterase inhibition achieved in CSF.

Mohs, Davis, Johns et al - Cognitive improvement in Alzheimer's from physostigmine correlates with hormonal evidence (cortisol) that physostigmine did get into brain.

Hollander, Kapell, Mohs et al - Reviews oral physostigmine studies. With multiple dose regimen, adequate dose, and recognition-type tests, 2/3 of patients respond.

Dysken - Good table. Nine of 11 physo studies at adequate dose are positive. Ergots, naloxone, lithium, peptides don't work.

Sano, Stern, Mayeux - Latest long-term physostigmine study. Nine of 13 pts. improved on at least 2 of 3 cognitive tests, increasing with time on drug.



Pharmacologic Properties of Galanthamine

Tonkopii and Prozorovskii - 1) Galanthamine is equipotent to THA in cholinesterase inhibition in brain slices in vitro. 2) Galanthamine inhibits brain cholinesterase for at least 2 1/2 hr. in the mouse despite plasma half-life in that species of 40 min.

Chaplygina and Ilyuchenok - Galanthamine reverses scopolamine-induced amnesia.

Sweeney, Hohmann, Bowersox et al - Galanthamine restores memory in mouse Alzheimer's disease model, testing done 3 1/2 hr. after intraperitoneal administration.

Mihailova and Yamboliev - 65% oral bioavailability, plasma peak 15 min, brain peak 20 min, plasma:brain ratio, 1:3.25, no evidence for variable plasma degradation (as with physo).

Westra, van Thiel, Vermeer et al - Plasma half-life in humans, 4 hr 23 min.

Toxicity Information

Stojanov - Anesthetic study. 2758 pts. Safe in heart disease, elderly. Alerting effects noted.

Wislicki - Updates Stojanov series at Sofia University Hospital to 6000 pts. by 1967.

Ikonomoff - 2000 women treated chronically, 160 followed for 4 years. No side effects.

Gujral - 109 children received 0.3 mg/kg daily for 40 d. Two rashes, 8 with GI distress, responsive to dose decrease.

Gopel and Bertram - (partial translation) 100 adults. 5-20 mg/d x 60 d, "well tolerated."

Michaelov, Zlateva, Dimitrov et al - Rabbits receiving 2.5 mg/kg/d x 5 months showed only reduction in atherosclerosis on histologic exam of organs.

Given the above data establishing the cholinergic deficiency in Alzheimer's disease, its correlation with the mental deficit, the reversal of that deficit by cholinergic agents which get into brain, galanthamine's activity as a long-acting cholinesterase inhibitor with excellent brain penetration, and its effectiveness in the mouse Alzheimer's disease model, it is hard for me to construct the "negative" scenario you requested. If this drug were not effective in Alzheimer's disease, I think that scientifically you'd have to question the study methodology before you questioned the drug.

Here's the best negative approach I can offer. About a third of patients has a severe noradrenergic deficiency in addition to the cholinergic deficiency. In fact, this group has a greater cholinergic deficiency than those without the noradrenergic deficiency. About a third has a mild noradrenergic deficiency. Data were presented at the ACNP in December that rats with a combined adrenergic/cholinergic lesion do not respond to cholinergic therapy alone. A noradrenergic agonist such as clonidine must be added to physostigmine before their cognitive deficit is restored. (Incidentally, an experimental somatostatin deficit does not need to be repleted for cognitive improvement.) Thus, only one third of patients, that is, those with a pure cholinergic deficiency, should be expected to have substantial responses to a cholinergic therapy alone. This is quite consistent with the 50% responsivity to THA noted in preliminary analyses of the National Institute of Aging's large scale replication of the Summers study. One should note, however, that all the Alzheimer's patients will require a drug such as galanthamine to reverse the cholinergic deficit first. Those who do not respond should then have a noradrenergic agent added. (This is of course an experimental issue at present.)

I do hope I (we) can find some way to make this drug available sooner than six years. Now that most people in this field have personally seen one or two patients with dramatic responses to THA, the current population of Alzheimer's patients cannot be allowed to die without ever receiving a trial of a cholinergic drug. Galanthamine is almost certainly safe enough for patients with Alzheimer's disease. It might be possible to obtain "fast track" status for galanthamine, given THA's liver toxicity.

Please do not hesitate to call for any question or comment you may have. I will attempt to provide you with required information as quickly as possible.

Thank you for your interest.

Yours truly,

Bonnie M. Davis

Bonnie M. Davis, M.D.

EXHIBIT 19

WYETH LABORATORIES INC. Wyeth P.O. Box 8299, Philadelphia, Pennsylvania 19101

February 3, 1988

Dr. Bonnie Davis
17 Seacrest Drive
Huntington, N.Y. 11743

Re: Galanthamine

Dear Dr. Davis:

Our clinical and pre-clinical people have reviewed the information that you provided to us on Galanthamine. They comment that this product had previously been reviewed within our organization in August of 1987 and also again late in 87. Unfortunately, we are still not able to express interest in this product. Our perspective is that the potential for success of tacarine and physostigmine and other anti-cholinesterase products is not very positive. With this information in-hand we are unable to make a commitment as relates to Galanthamine. It is my impression that there may be some meetings later this year which address the potential efficacy of these compounds. If in fact some solid data is obtained we may want to re-open discussion with you about Galanthamine.

Thank you for thinking of Wyeth-Ayerst. I trust you will have success in finding a licensing outlet for this product.

Best regards,

William A. Cressman, Ph.D.
Asst. Vice-President
Licensing & Business Development

WAC/edr

Plaintiff's Exhibit
PX - 596

read 3/19/88 by me

Dr. Bonnie Davis
17 Seacrest Drive
Huntington, N.Y. 11743

Wyeth

P. O. BOX 8299, PHILADELPHIA, PA. 19101

E-1218

EXHIBIT 20

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Survey of Treatment Attempts in Senile Dementia of the Alzheimer Type

L.E. HOLLISTER

Professor of Medicine, Psychiatry and Pharmacology, Stanford University School of Medicine and Senior Medical Investigator, Veterans Administration Medical Center, Palo Alto, CA

A quiet epidemic of senile dementia of the Alzheimer type (SDAT) has been attributed to the increasing age of the population of Western countries (1). About 2 to 3 million elderly individuals in the United States have senile dementias and uncounted others suffer from milder cognitive loss. As the number of elderly increase over the next few decades, so will the number of those with SDAT.

Drug treatments for psychoses associated with old age have not been notably successful. Problems in evaluating drug therapy are considerable, for one is often dealing with a complex interplay of psychosocial, brain, and general physical disorders. Some of these factors may fluctuate, while others are progressive. The contribution of each of these multiple factors to the total degree of disability is difficult to weigh. Many studies to evaluate drug therapy are performed in patients so deteriorated that it would take a miracle to show much positive benefit. In any case, gains are likely to be small and may take a while to become apparent.

Drug Therapy: Symptomatic

Symptomatic treatment is the most useful drug therapy. Small doses of antipsychotic drugs, either alone or combined with anxiolytics, may curb disturbed behavior, improve self-care and restore a normal sleep-wake cycle (2). Such purely symptomatic improvements are highly valued by those charged with the care of these patients. About 8-15 percent of patients with SDAT are also derpessed, a treatable condition. Tricyclic antidepressants may predispose to the development of delirium, due to their anticholinergic action, and make the patient worse. Monoamine oxidase inhibitors might be a better choice, but orthostatic hypotension limits their applicability. Some of the newer antidepressants that lack anticholinergic or adrenoreceptor blocking actions may be more useful, but experience is limited.

Doses of antipsychotics, such as haloperidol, might begin with 0.5-1.0 mg/day with small increments until control of behavior is achieved. Doses of tricyclic antidepressants should start with 10 mg/day; usually less than 100 mg/day will be adequate for most patients. Doses of diazepam should begin with 2 mg/day at night and probably need never exceed 10 mg/day.

Drug Treatment: Obsolete

In the days when deficiency diseases were newly recognized, whether due to vitamins or hormones, it was easy to postulate that a variety of vitamins or hormones might remedy SDAT. None had any rationale and none was beneficial. Stimulants and analeptic agents were used, with a great deal of emphasis on pentylenetetrazole, but clinical trials were unconvincing. The idea that long-term memory might be encoded in brain ribonucleic acid (RNA) led to the futile use of yeast RNA taken orally (Table).

Current interest centers around a drug called Gerovital H-3, which turns out to be procaine hydrochloride in a special pharmaceutical preparation with benzoic acid, said to increase its stability and oral absorption. The few reports in the U.S. literature damn it with faint praise. Its main effect seems to produce mild euphoria, which might be part of a mild antidepressant action attributable to the fact that it is a mild inhibitor of monoamine oxidase (3).

Drug Therapy: Vasodilators

Early studies suggested that blood flow was decreased in the brains of senile patients. This observation led to the idea that many cases of senility were due to cerebral arteriosclerosis. This idea, in turn, led to the employment of many types of vasodilators for treatment of senile dementias. Except in the case of "multi-infarct" dementia, which probably accounts for only 10-15% of cases of senile dementia, the role of cerebrovascular changes in producing dementias is not currently held to be of much importance. Any diminution in cerebral blood flow in senile dementia is more likely the consequence of diminished cerebral metabolism due to loss of neurons.

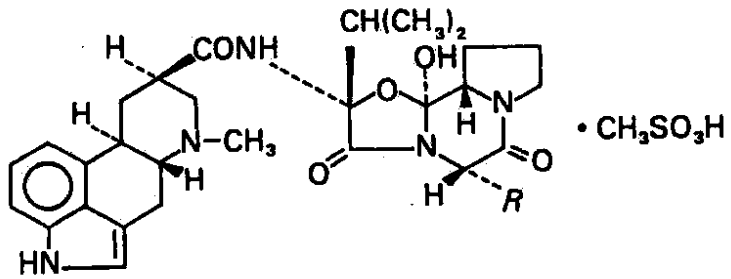
Of the various vasodilators (Table), papaverine has been most studied. Results of treatment with this drug are often no better than the placebo controls (4). Cyclandelate and isoxuprine have been studied less, with similar unconvincing evidence. One might postulate that drugs such as these, which also dilate blood vessels peripherally, might actually decrease the brain circulation by stealing blood from the brain to the periphery.

The vasodilator of greatest current interest is pentoxyfylline. This homologue of theophylline is believed to exert a beneficial rheologic effect by increasing the deformability of erythrocytes. Thus, passage of red blood cells through the microcirculation would be improved. The clinical usefulness of this drug in SDAT is still under investigation.

Drug Therapy: "Metabolic Enhancers"

Some drugs have been found, either in vitro or in vivo, to protect brain against altered functions imposed by experimental injuries, such as ischemia, anoxia, nutritional deficiency and the like (Table). Ergoloid mesylates, formerly classified as a vasodilator due to its adrenoreceptor blocking action, is now considered to work by protecting altered brain metabolism (5). This drug, which has been in clinical use for almost three decades, has the most extensive body of experimental support for its efficacy, yet many unanswered questions remain (Figure 1).

STRUCTURE OF ERGOLOID MESYLATES



	R
Dihydroergocornine	$-CH(CH_3)_2$
Dihydroergocristine	$-CH_2C_6H_5$
Dihydro- α -ergocryptine	$-CH_2CH(CH_3)_2$
Dihydro- β - ergocryptine	$-CH(CH_3)CH_2CH_3$

The compound is a mixture of related ergot derivatives with a peptide component.

Fig. 1. — Structure of ergoloid mesylates. The compound is a mixture of related ergot derivatives with a peptide component.

One of the most important of these is whether or not the drug is efficacious. Many clinicians doubt the clinical efficacy of ergoloid mesylates and do not use it at all. Yet in reading the literature one is struck by the fact its efficacy is as well proven as it is for almost any drug used for treating psychiatric disorders. At the time of a 1979 review, some 33 clinical evaluations of ergoloid mesylates in senile dementia had been published, 22 of which

were controlled clinical trials that met standard criteria for being adequate (4). All of these 22 trials noted statistically significant improvement on some behavioral or psychological measure among patients treated with this drug.

Assuming that the drug may be effective, even though the percent of patients showing clinically significant improvement is small, the proper daily doses and duration of treatment have also been marked by uncertainty. Over the years the daily doses used for treatment have varied from 3-12 mg, with 4.5-6.0 mg currently favored. Bioavailability of the drug is so small that only microgram amounts of drug enter the systemic circulation following individual doses. Duration of treatment to test clinical efficacy has usually been 3 months although 6 months may be better. Yet even the latter period of time is inadequate to test whether the drug protects against progressive decline.

Among the new so-called metabolic enhancers, piracetam has aroused the most interest. It is a homolog of gamma-aminobutyric acid, an inhibitory neurotransmitter in the brain. The term "nootropic" has been coined to describe its presumed ability to enhance memory and learning. A number of clinical studies have been positive, to the same degree as to ergoloid mesylates.

One controlled clinical evaluation of piracetam in 60 elderly psychiatric patients (precise diagnoses not specified) found increased alertness as the most obvious change in those patients treated for 12 weeks either with 2.4 or 4.8 g/day of the drug (6). Another study used both normal volunteers as well as symptomatic volunteers (that is, people over 50 years of age with memory problems) and found improved memory after 12 weeks of treatment (7). The drug seems to be devoid of side effects. Other uses of the drug have been to reduce the impairment of consciousness following brain surgery, to reduce memory impairment following electroconvulsive therapy, to treat both naturally-occurring and drug-induced Parkinsonism, and to alleviate central vertigo. Newer homologs of piracetam are in the process of development by several pharmaceutical companies due to its promising clinical actions (Figure 2).

Nafronyl has been marketed in Europe for over 10 years in the treatment of peripheral vascular diseases and SDAT. Eight double-blind clinical trials in Europe have shown positive results in SDAT. Experience with this drug in the United States has thusfar been limited.

Drug Therapy: Investigational

For a number of years, neurochemical studies in the brains of patients with SDAT have indicated a severe deficiency of acetylcholine and the enzyme responsible for its synthesis, choline acetyltransferase (8). Other neurotransmitters, such as dopamine, serotonin, and norepinephrine are also decreased, possibly due to an increase in the activity of monoamine oxidase, or simply the drop-out of neurons. The deficiency of acetylcholine has been

PIRACETAM AND RELATED CHEMICAL STRUCTURES

STRUCTURAL RELATIONSHIPS OF PIRACETAM AND SOME HOMOLOGS

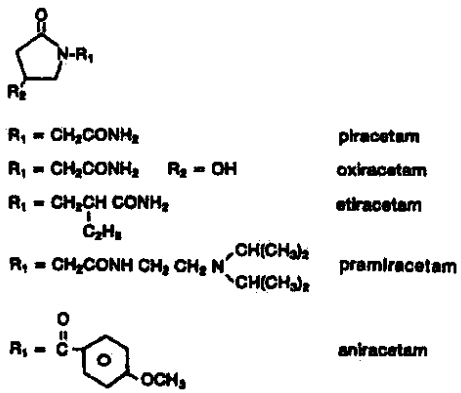


Fig. 2. — Piracetam and related chemical structures.

much more prominent. It is probably due to a marked loss of neurons in the basal nucleus of Meynert, the most important cholinergic projection to the hippocampus and the forebrain (9). Using the analogy to Parkinson's disease, where increasing a deficient neurotransmitter has therapeutic benefits, attempts are now being made to increase acetylcholine in the brains of patients with SDAT. The use of precursors, such as choline or lecithin, has not been marked with much success (10). Recently, reports of success with acetylcholinesterase inhibitors, such as physostigmine, have aroused considerable interest (11). Such treatment is not easy to provide and has some potential hazards, so it may be some time before we know whether it merits clinical use (Table).

Recent detailed reviews of the role of neuropeptides in the central nervous system and in cognitive function have appeared (12). Two general categories of peptides have attracted most attention; those secreted by the pituitary, (namely adrenocorticotropic hormone, melanocyte stimulating hormone and vasopressin) and the enkephalins (Table). Currently most of the attention has settled on the 4-10 fragment adrenocorticotropic hormone and vasopressin homologs which have been tested with mixed results in geriatric populations. These approaches to treatment are still highly experimental.

Non-drug Therapy

Proper psychosocial interventions not only are helpful but obligatory. It is far easier to consider senile patients as totally out of touch than it is to continue to maintain a supportive and caring environment. Frequent personal contact, expressions of attention, and attempts to keep the patient in touch with the world (perhaps with a discussion of the daily news, alluding frequently to the day of the week, the date, the month and the year) are ways in which some of the social withdrawal and isolation can be mitigated. Such care, alas, may tax all the resources of the most dedicated family and its purchase is terribly dear. Unfortunately, the aims of treatment of most nursing homes are simply to keep the senile patient quiet and dry.

Based on a lingering notion that senile dementias may be associated with hypoxemia, attempts have been made to treat the disease with hyperbaric oxygen. A small controlled trial of this approach yielded negative results (13). Little current interest persists.

Summary

Treatment of SDAT is presently far from satisfactory. Many physicians have taken such a negative view of the prospects that they refuse to try anything. If one wishes to do the best that is possible for a patient, it would seem that a trial of the more promising existing drug treatments, such as ergoloid mesylates or piracetam, would be justified. The investment is small. One should also try to provide the best possible supportive care.

The urgency of the problem of SDAT has prompted action on many levels. Major pharmaceutical companies now have active programs to seek new drugs that may be better than the few currently available. One would hope that they will be as successful in this area as they have been in so many others.

TABLE

DRUGS FOR SDAT: OBSOLETE

vitamins, glutamic acid
hormones - thyroid, adrenal, gonadal
RNA - yeast RNA
procaine - Gerovital H-3

DRUGS FOR SDAT: VASODILATORS

cyclandelate
papaverine
isoxuprine
pentoxyfylline

DRUGS FOR SDAT: "METABOLIC ENHANCERS"

ergoloid mesylates
piracetam, homologs
nafronyl

DRUGS FOR SDAT: EXPERIMENTAL

Neurotransmitter enhancers

physostigmine, tetrahydroaminacrin - cholinesterase inhibitors
arecoline - cholinergic agonist

Neurotransmitter precursors

choline, lecithin -? acetylcholine
levodopa - dopamine
tryptophan - serotonin
phenylalanine -? norepinephrine

Neuropeptides

ACTH fragments
vasopressin homologs
somatostatin
enkephalins

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Treatment of Alzheimer's disease: new outlooks for the future

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Present therapeutic efforts in Alzheimer's Disease (AD) are based on either of two concepts: *first*, that one or more neuronal pharmacosystems are malfunctioning, whether they are intact or are partially depleted of neurons (1); *second*, that cerebral metabolism is diminished in a non-specific way(s). Drugs that enhance neurotransmitter function in remaining neural circuits have been tried in an effort to overcome the first hypothesized mechanism; metabolic enhancing agents, or "nootropic" drugs have been used to deal with the second (3).

Despite sporadic reports of barely detectable improvements with various drugs or drug combinations, therapeutic efforts have, in general, failed to produce improvement of clinical value. It is well to remember that, except for the extraordinary therapeutic success of dopaminergic agonists in Parkinsonism, no other degenerative neurologic disorder has responded to a similar strategy. We must, therefore, consider other therapeutic approaches that depend on different concepts of the etiology and pathogenesis of AD.

Our present knowledge of the cause of AD, and the mechanism by which its brain changes produce dementia is scant. The most likely possibilities are:

1) AD is a *degenerative disorder*, linked to aging, with *genetic loading*, influenced by *environmental factors* (2);
2) Ad causes both *losses* of neural elements, and *dysfunction* in remaining ones;
3) Ad affects neural elements both in a *diffuse* pattern, and more severely in *selectively vulnerable* systems.

Ideal therapeutic strategies would attack the underlying etiology of AD, preventing the pathogenetic process — be it biochemical or viral, toxic or genetic — from damaging the brain. Such approaches are wishful at best until we know more about the etiology of AD. *Secondary* strategies would attempt

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Aspects on Etiology, Pathogenesis, Diagnosis and Treatment

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II: Diagnostic and treatment aspects

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EXHIBIT 21

The Cholinergic Hypothesis: A Historical Overview, Current Perspective, and Future Directions

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INTRODUCTION

When one considers that Alzheimer's disease was initially characterized in the first decade of this century,[1] it seems remarkable that the disease remains such a mystery. The relative etiologic roles played by various genetic, toxic, viral, and immunologic influences remain ill-defined, and the origin and direct functional implications of its most characteristic neuropathological markers, neurofibrillary tangles and amyloid plaques, likewise are unknown. Although it has been shown that inadequate blood supply to the brain does not provide a tenable explanation for the primary symptoms of Alzheimer's disease,[2] the final neurological pathways that are responsible remain obscure.

One possible exception to this is the recent accumulation of evidence suggesting that a breakdown of central cholinergic transmission plays an important role in the earliest and primary symptoms of the disease, manifested as a severe and progressive cognitive disturbance highlighted by an inability to remember recent events.[3-5] With normal aging, a similar, though less severe, memory loss has been documented[6,7] (sometimes referred to as benign senescent forgetfulness[8]) with similar evidence for a parallel role of cholinergic dysfunction.[6,7,9,10] The logic and empirical support for this line of thinking have collectively become known as the "cholinergic hypothesis of geriatric memory dysfunction."[3-7] Stated in its most simple and direct terms, the cholinergic hypothesis asserts that significant, functional disturbances in cholinergic activity occur in the brains of aged and especially demented patients, these disturbances play an important role in the memory loss and related cognitive problems associated with old age and dementia, and proper enhancement or restoration of cholinergic function may significantly reduce the severity of the cognitive loss.

One should note that the cholinergic hypothesis states nothing about etiological factors responsible for aging or dementia. Rather, it attempts to explain only the most direct, cause-effect relationship associated with the primary symptoms (i.e., memory loss). Likewise, the hypothesis does not address the additional roles that cholinergic dysfunction may play in other neurobehavioral disturbances of aging or dementia. Finally, no exclusive or solitary involvement of the cholinergic system in age-related

memory loss is implied, for it is commonly acknowledged that other neurotransmitter systems are also, most probably, involved. However, the hypothesis does imply that the existence of relationships between neurotransmitter dysfunction and age-related memory loss is most clearly established with respect to the cholinergic system. The testing and establishment of similar relationships for other neurotransmitter systems remain among the challenges of future research.

During the last four to five years, basic and clinical research efforts directly and indirectly related to the cholinergic hypothesis have accelerated rapidly. This increased interest presumably is related to a growing recognition of the enormous socio-economic problems confronting our society as our population continues to age. The additional emotional and financial burdens imposed by age-related cognitive decline, especially the severe decline associated with Alzheimer's disease, contributes further to this interest. From this perspective, the primary significance of research concerned with the cholinergic hypothesis is based upon the presumption that greater insight into the common neural pathways responsible for the cognitive disturbances may eventually lead to effective therapeutic treatment of the problem.

Because of the rapid development of thinking in this area, and the continuing intensive research activity and controversy it provokes, a cohesive overview of progress and issues might be useful. The present paper, therefore, will attempt to provide a brief historical overview of the research and ideas that gradually evolved into the current cholinergic hypothesis, offer some perspective upon current thinking and research efforts in the area, and finally, provide a loose conceptual framework and specific suggestions for future work.

HISTORICAL OVERVIEW AND CURRENT PERSPECTIVE UPON THE CHOLINERGIC HYPOTHESIS

Early Historical Foundation

What the cholinergic hypothesis may lack in definitive, quantitative evidence, it enjoys in the diversity and breadth of its support. The initial empirical foundation for the cholinergic hypothesis can be traced to at least four distinct areas of study: biochemical determinations of human brain tissue, particularly from Alzheimer's patients; animal psychopharmacological studies; clinical pharmacological observations; and (for lack of a better descriptor), basic neuroscience research. Starting from these four somewhat independent areas of investigation, thinking and research directives evolved relatively rapidly, converging into a mutually corroborated network of circumstantial support.

By the mid-1960s, seminal findings in all four areas generated sufficient evidence to support some of the initial integrative concepts of the cholinergic hypothesis. As shown in TABLE 1, early predescendent clinical teachings recognized that drugs blocking central cholinergic activity produced a dementia-like syndrome, with concomitant memory loss.[11–13] Indeed, one popular means of facilitating childbirth in the 1950s and 1960s involved giving a relatively light dose of a sedative or hypnotic simultaneously with a central anticholinergic, producing a state of consciousness defined as "twilight sleep."[14] An important and interesting characteristic of this condition was a marked reduction in the ability of patients to remember events occurring just prior to and during the operation.[15,16] Interestingly, this phenomenon and therapeutic application was described very early in this century,[14] coincidentally close in time to when Alzheimer published his classic case study characterizing the disease which now bears his name.[1]

TABLE 1. Abbreviated Conceptual/Empirical History of Cholinergic Hypothesis

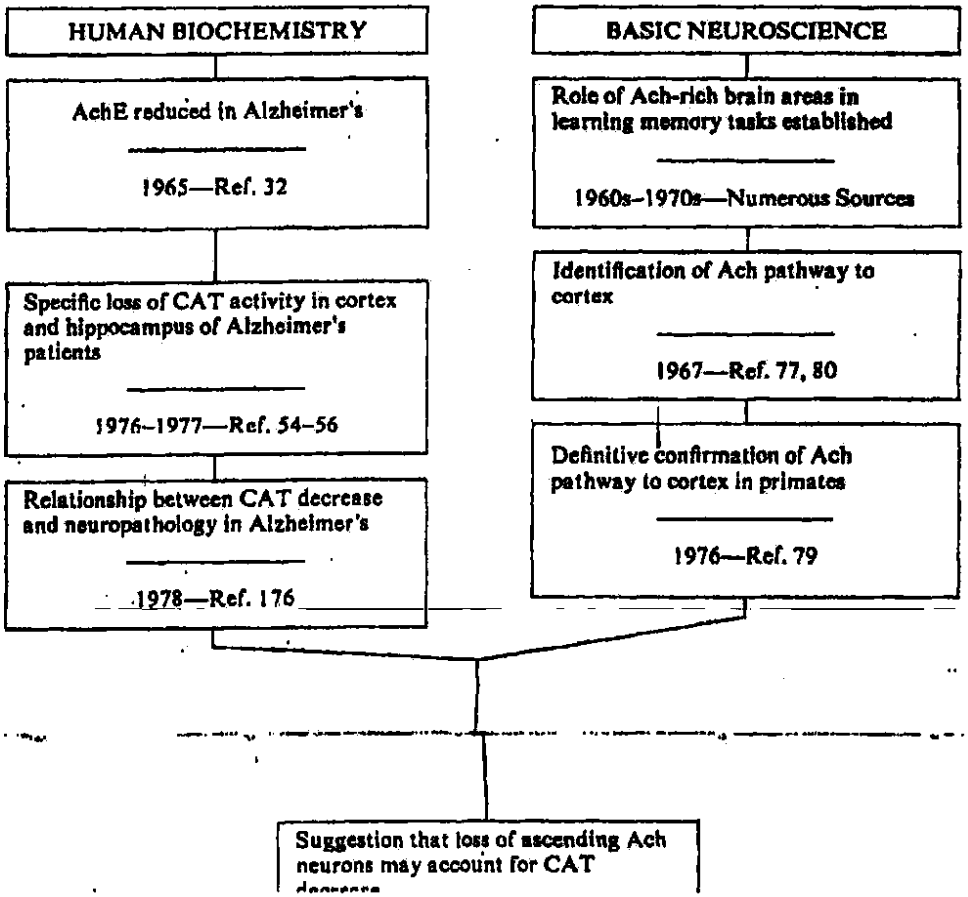

TABLE 1 *Continued*

TABLE 1 *Continued*

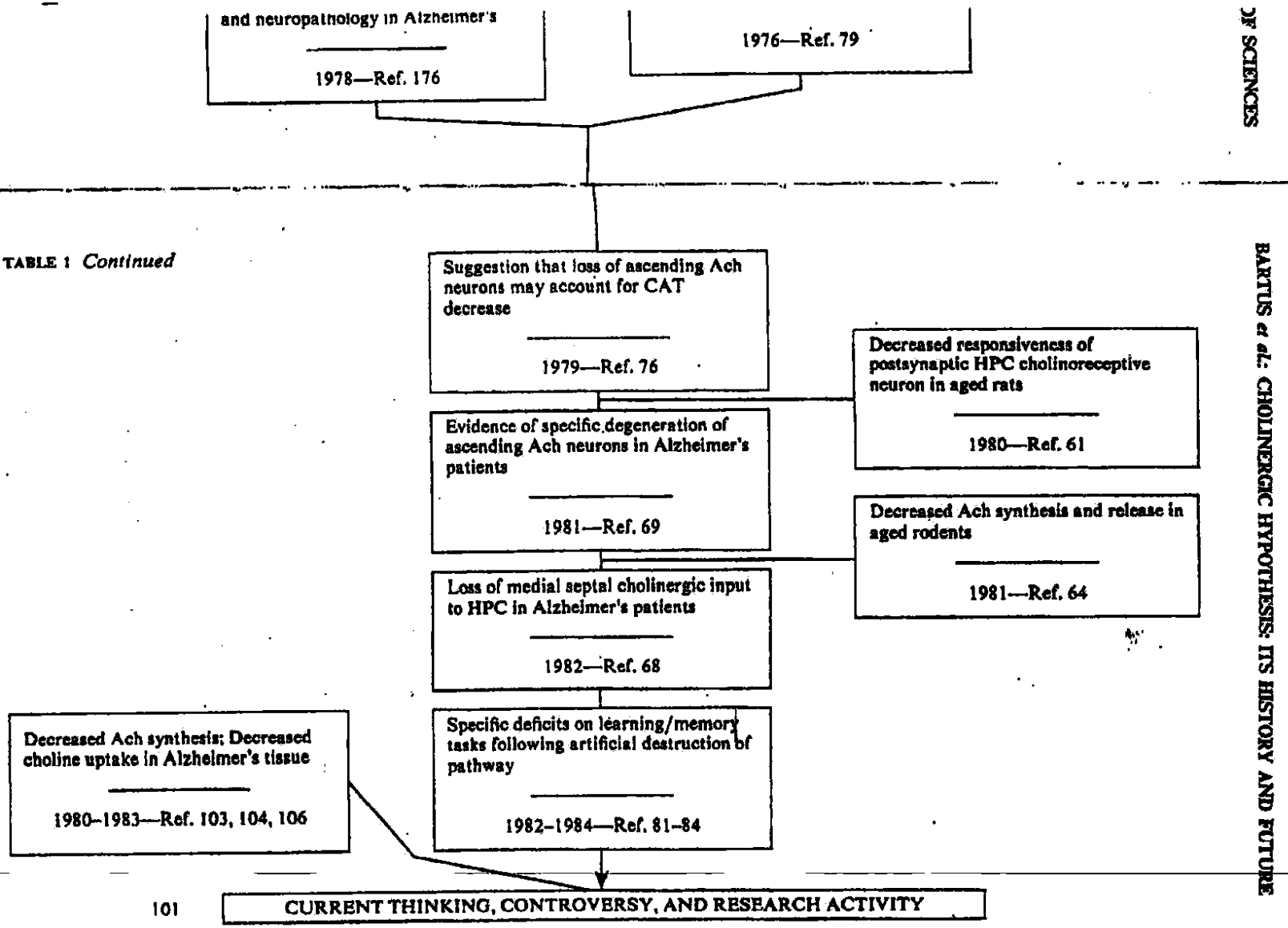

TABLE 1. Continued

1977—Present

Positive but variable dose-response effects of physostigmine on memory in aged monkeys

1978–1979—Ref. 131, 177

Positive but variable effects of physostigmine confirmed in aged patients

1979—Ref. 134

Potential superiority of muscarinic agonists suggested

1980—Ref. 139

Preliminary confirmation of agonist benefits in Alzheimer's patients

1982—Ref. 136

Advantages of improving multiple neurochemical disturbances

1979–1980—Ref. 150–159

CURRENT THINKING, CONTROVERSY, AND RESEARCH ACTIVITY

In the animal psychopharmocological literature, early work in the 1960s characterizing the behavioral effects of centrally acting drugs, began to generate support for an important role of cholinergic activity in learning and memory.[13,17–19] Most notably, Herz[20] and Meyers and Domino,[21,22] suggested specifically that one effect of blocking cholinergic function in the central nervous system may include an impairment of recent memory. The systematic studies of Deustch and colleagues[17,18] helped demonstrate a clear role for cholinergic-sensitive neurons in mediating learning and memory. Their publications played a key part in establishing general acceptance of this idea.

Similarly, the basic neuroscience research of the same era began to demonstrate that brain regions now known to be rich in cholinergic neuronal elements (e.g. hippocampus, septum, amygdala, and frontal cortex) seemed to play important roles in learning and memory phenomena.[23–27] Indeed, it is interesting to note that in one of the earlier studies of the effects of anticholinergics, it was speculated (on the basis of the nature of the behavioral results) that a hippocampal site of action may mediate the anticholinergic memory deficits observed.[22] The existence of dense fields of muscarinic receptors in the hippocampus was not confirmed neurochemically for another decade.[28–31]

Finally, attempts to characterize changes in the brains of Alzheimer's patients led to the observation of significantly reduced acetylcholinesterase (AChE) activity by Pope *et al.*[32] However, because of general controversy regarding the specificity of this marker and the lack of attention paid by the authors toward the reduced AChE activity, this paper remained relatively obscure until recently.

Later Pharmacological Studies

The first formal suggestion that the specific cognitive effects of age may be similar to the cognitive effects of anticholinergic drug treatment (in young subjects) was published by Drachman and Leavitt.[33,34] Interestingly, Crow and Grove-White[35] independently suggested a relationship between anticholinergic memory loss and Korsakoff's amnesia a year earlier. Drachman and Leavitt[34] demonstrated that young subjects given an acute dose of scopolamine performed various tasks of a cognitive test battery in a manner similar to normal elderly subjects. They concluded that the selective performance failures on certain memory tests that are observed in elderly subjects may therefore be related to a cholinergic deficiency in aged brains. Others have since drawn similar parallels between the memory loss of Alzheimer's patients and the effects of anticholinergic drugs in young subjects.[36,37]

Soon after the Drachman study, a series of papers was published showing similarly parallel memory deficits in aged monkeys and scopolamine-treated young monkeys.[38–40] In addition, scopolamine's age-mimicking effects upon memory were shown to be at least somewhat specific to its effects on central muscarinic receptors, since similar age-like effects on memory were not obtained with a number of other drug treatments, including dopaminergic and alpha-adrenergic blockers,[40,41] several nonspecific and catecholaminergic stimulants,[42] nicotinic receptor blockers,[43] and peripheral anticholinergics.[43] Although most researchers readily acknowledge that other neurochemical systems must also be involved in the mediation of recent memory, few non-cholinergic pharmacological agents have yet been identified that also produce specific, age-similar effects on memory performance. The two most notable exceptions, observed in both human and non-human primates, are diazepam and tetrahydrocannabinol.[43–48] Interestingly, both drugs show evidence of interacting directly or indirectly with cholinergic neurons.[49–53]

Determinations from Alzheimer's Brains

During the time these drug studies in humans and animals were being conducted, independent neurochemical assessments were being performed on postmortem tissue from brains of Alzheimer's patients. Bowen *et al.*[54] first published evidence that choline acetyltransferase (CAT) activity was reduced in Alzheimer's patients (relative to age-matched controls). Further, they observed that the reduction was widespread (involving several brain regions), that some degree of specificity existed (since markers from other neurotransmitter systems were not similarly reduced), and that the decrease in CAT activity may be correlated with loss of cognitive function and density of plaques and tangles. Very soon after, similar findings were published by Davies and Maloney[55] and Perry *et al.*[56] Thus, within a period of a few months, three British laboratories independently reported that the brains of patients with Alzheimer's disease exhibited a profound (and somewhat specific) loss of CAT activity upon postmortem examination. These initial observations were soon followed by a flood of papers confirming the basic findings.[3,4] Observations of decreases in CAT activity ranging from 50 to 80 percent are now quite common in brains from Alzheimer's patients.[3]

Although the loss of CAT activity gained widespread acceptance as an important characteristic of Alzheimer's disease, other mysteries emerged. For example, the neural mechanism through which the loss of CAT activity might play a causative role in the functional declines of Alzheimer's disease (especially the loss of cognitive ability) remained unclear. It has been known for some time that CAT is not a rate-limiting enzyme for acetylcholine synthesis,[57–59] for inhibition of greater than 90 percent of available CAT produces only nominal effects on acetylcholine synthesis *in vitro*. How then might one entertain that a loss of only 50 to 80 percent of CAT activity could be responsible for the devastating loss of cognitive capacity? Two mutually compatible explanations have emerged. The first was primarily logical and recognized that, in addition to the dementia-specific decrease in CAT activity, most Alzheimer's patients possess additional decreases in cholinergic function characteristic of normal aging.[3] Thus, it was deduced that the collective co-existence of certain age-related disturbances, such as reduced post-synaptic cholinergic responsivity[60–62] and impaired synthesizing capacity of ACh neurons,[63,64] may create a condition where the additional, profound loss of CAT activity produces substantial functional consequences. In other words, it was suggested that although the loss of CAT activity alone may not normally be sufficient to reduce overall cholinergic function, when the loss is added to an already impaired system, additive (or possibly synergistic) functional impairments should result.[3]

More recently, postmortem histological observations from Alzheimer's brains demonstrated that many demented patients may suffer a significant deterioration of neurons originating in the nucleus basalis of Meynert and the septum.[65–72] These brain regions are known to provide the primary cholinergic input to the hippocampus and cerebral cortex,[73–80] areas that suffer major loss of CAT activity in Alzheimer's brains.[3,4,54–56] Thus, it is possible that the loss of CAT activity reflects a degeneration of cholinergic neurons projecting to the cortex, as opposed to a proportional decrease of CAT activity within individual, functionally intact neurons. The consequences of such extensive neuro-degeneration would be expected to produce a profound disruption of central cholinergic function far beyond what would be predicted by the effects of inhibiting CAT activity *in vitro*.

Recent reports in rodents demonstrating that specific destruction of homologous cholinergic neurons in the basal forebrain produces specific impairments on memory tasks[81–84] add further support to the concept that cholinergic degeneration may be

causally linked to cognitive dysfunction in elderly humans. However, as discussed later in this paper, certain caveats must be recognized before hypothesizing any simple, cause-effect relationship between cholinergic degeneration and memory loss.

More Recent Studies of Cholinergic Dysfunction

While many laboratories in the latter half of the 1970s focused on the pathological changes correlated with Alzheimer's disease, others concentrated on identifying and defining functional impairments in the cholinergic system that might be partly responsible for the cognitive impairments of age and dementia. Many of these studies are listed in TABLE 1, but some of the more noteworthy include evidence for specific decreased responsiveness to acetylcholine by hippocampal pyramidal cells of aged rats,[60-62] loss of acetylcholine-synthesizing capacity in brains of aged rodents *in vivo*,[63,64,102] and loss of acetylcholine-synthesizing capacity of biopsy tissue of Alzheimer's patients.[103,104]

Research directed toward other phenomena, such as changes in muscarinic receptor density and high affinity choline uptake,[103,105-111] remains controversial or inconclusive. Certainly, substantial work remains to be done before a sufficient understanding of the nature of the cholinergic dysfunction associated with aging and dementia (as well as differences between the two) is established. Nevertheless, a remarkable amount of information has been generated during the last six years, and little doubt can remain that there are significant reductions in numerous aspects of cholinergic transmission in the aged brain and that additional changes are associated with Alzheimer's disease.

Evidence for Interacting Non-Cholinergic Influences

It should be noted that changes in other neurotransmitter markers and degeneration of noncholinergic neurons have also been reported in brains of Alzheimer's patients. These include various changes in noradrenergic,[85-88] dopaminergic,[85,89,90] serotoninergic,[86,91] and somatostatin[92-95] markers, as well as evidence for profound degeneration of noradrenaline-containing neurons of the locus coeruleus.[96-99] However, the significance of these changes to the cognitive loss of Alzheimer's disease remains unclear and somewhat controversial. Some of the alterations (such as decreases in dopamine markers) have not been consistently reported,[55,86,97,100,101] while others (e.g. degeneration of locus coeruleus), appear to be present only in presumed subpopulations of patients lacking independent identification.[99] Further, it has been argued that many of these changes are due to improper patient screening procedures, resulting in the inclusion of patients with multiple diseases (such as concomitant Parkinson's disease or clinical depression), making any interpretations specific to Alzheimer's disease problematic.[5] Finally, additional problems of interpretation exist due to necessary focusing on the end-stage condition of the brains of Alzheimer's patients.

However, even if one accepts the accuracy and reliability of these changes, their contribution to the memory loss of Alzheimer's disease remains virtually untested. That is, simply demonstrating that significant changes in a particular neurotransmitter system occur in Alzheimer's disease or aging does not establish a relationship between those changes and loss of any behavioral functions, including memory. Considerably more multidisciplinary work is required to confirm and corroborate possible functional relationships before insight can be gained and conclusions drawn about a possible role in the cognitive loss of Alzheimer's disease.

Early Attempts to Improve Memory via Cholinomimetics

Although these functional studies of cholinergic dysfunction have contributed significantly to the idea of an important cholinergic role in age-related memory loss, the question of whether this line of thinking could serve as a starting point in the development of therapeutically significant effects remained in doubt. While skeptics criticized the cholinergic hypothesis as inherently simplistic, advocates pointed out the apparent analogy to the dopamine deficiency hypothesis of Parkinson's disease and the success of L-dopa in treating the symptoms of that disorder.[112,113]

Almost from the inception of the cholinergic hypothesis, clinicians were eager to test the corollary that cholinomimetics might be effective in the treatment of memory problems associated with Alzheimer's disease and aging. These attempts can be classified into one of three approaches: precursor therapy, anticholinesterase treatment, and muscarinic receptor agonist treatment. Because cholinergic precursors have a wide margin of safety, and relatively loose government regulations associated with their use, the vast majority of these studies adopted a precursor therapy approach. The impetus for this approach was derived from the observation that choline availability (unlike CAT activity) normally is rate-limiting for acetylcholine synthesis.[58,59] Cohen and Wurtman,[114] and Haubrich *et al.*[115] independently demonstrated that acute injections of choline chloride produced a significant, transient effect on brain acetylcholine levels in rats and guinea pigs. It was later shown that increasing dietary choline chloride[116] or lecithin[117] (a normal dietary source of choline) also significantly increased levels of brain acetylcholine. Thus, it was suggested that cholinergic function might be therapeutically enhanced by precursor treatment.[118,119] The rationale of these precursor studies was therefore straightforward and conceptually similar to that used to treat other neurobehavioral disturbances with precursor loading techniques.[119,120]

Nonetheless, scores of clinical trials have failed to demonstrate beneficial cognitive effects with either choline or lecithin in demented or nondemented aged patients.[3,122] In fact, it had been noted that certain assumptions inherent in this rationale, especially when applied to geriatric patients, had never been tested and may not be true.[3,121,122] These involve issues concerning the overall functional condition of the cholinergic system in aged brain and its ability to utilize extra exogenous choline in a functionally meaningful manner. Indeed, recent observations of decreased high affinity choline uptake in Alzheimer's brain,[103,106] reduced acetyl Co A production,[123] presynaptic neuronal degeneration,[65–72] and numerous other disturbances in normal aging and Alzheimer's disease provide empirical support for this caution. As we continue to generate data, perceptions gained from the benefit of hindsight make this approach seem less and less viable, although possible prophylactic benefits[121,124–126] remain primarily untested.

By contrast, the testing of cholinergic agonists and cholinesterase inhibitors as a means of improving geriatric memory has not been as extensive as precursor therapy, but has been somewhat more successful. To date the most popular cholinomimetic has been the anticholinesterase physostigmine. Early studies with young adults reported moderate improvement in cognitive tasks within a very restricted dose range.[127] Those doses outside this narrow range produced either no change in performance or marked impairment. Although initial attempts to demonstrate improvement with physostigmine in geriatric patients were not successful,[128–130] it is now generally accepted that physostigmine can improve geriatric memory. However, the effects are quite subtle, requiring strictly controlled test conditions and special attention to large individual variations in the most effective dose.[131,132] Furthermore, the most consistent effects have been obtained with intravenous injections of the drug.[132–136] Thus, despite the

theoretical importance of these data, their direct therapeutic relevance remains in doubt.

More recently, preliminary evidence suggests that the oral form of physostigmine may not require as much attention to individual differences in most effective dose.[137] However, this suggestion requires confirmation[138] and there is no *a priori* reason to believe that the therapeutic effects of oral physostigmine should be more robust than those obtained with systemic injections.

The final class of cholinergics to be considered are those drugs that directly stimulate central muscarinic receptors. Recent reports that degeneration of cholinergic forebrain nuclei may account for the loss of CAT activity in Alzheimer's patients provides additional impetus for studies with cholinergic agonists. That is, if one assumes this degeneration plays a major role in the cognitive symptoms of the disease, then the most effective means available to treat the deficit would be to compensate for the loss of cholinergic input to the cortex and hippocampus by stimulating the surviving postsynaptic receptors with direct muscarinic agonists. Certainly drugs requiring functionally intact, presynaptic cholinergic terminals (such as cholinergic precursors and anticholinesterases) should be less capable of improving cholinergic tone or restoring the balance of the central nervous system than are drugs that interact with postsynaptic cholinergic receptors. Although relatively few studies with muscarinic agonists have been performed, the earlier tests have provided additional (albeit modest) support for using cholinergic stimulants to improve geriatric memory. When the direct muscarinic agonist arecoline was tested in aged monkeys, not only was significant improvement obtained in a delayed recall task,[139] but the dose response effects were also more consistent from monkey to monkey, as compared to physostigmine. Similar results have also been reported with Alzheimer's patients.[136] Clearly, additional clinical tests are required.

By way of contrast, other tests evaluating the dopamine receptor agonist apomorphine, GABA receptor agonist muscimol, and the alpha-adrenergic receptor agonist clonidine, have failed to produce any significant effects in aged monkeys.[140] Taken together, these initial tests in aged monkeys and Alzheimer's patients suggest that muscarinic agonists may provide a more effective means for treating the memory losses associated with aging and dementia than that provided by anticholinesterases, cholinergic precursors, and certain agonists acting upon other neurotransmitter receptors. However, none of these possibilities can be excluded conclusively at this time. Clearly the pharmacological studies supporting the superiority of cholinergic agonists remain sparse and tentative and require additional tests and comparisons.

At the same time, the degeneration of basal forebrain cholinergic neurons remains controversial and its implications are unclear. For example, recent studies have questioned the consistency and severity of the degeneration in Alzheimer's patients that was originally reported.[65,141,142] Moreover, others have reported significant loss of cells in the nucleus basalis of Meynert in several other clinical maladies, some of which are presumably unrelated to Alzheimer's disease.[65,66,143–145] Furthermore, the functional consequences of degeneration of these neurons have yet to be defined. Lesion studies in animals have only recently begun (see later section), and no detailed attempt to correlate degree of degeneration with cognitive loss in demented and non-demented subject populations has yet been reported. Finally, even assuming a significant and functional role of cholinergic cell death in age-related memory loss, the possibility still exists that increasing acetylcholine release from surviving neurons might provide an effective means of treating memory problems in aging and dementia. Recent preliminary reports support this possibility, with evidence of enhanced cholinergic function in rodents[146,147] and improved performance in aged rats[148] and Alzheimer's patients[149]

treated with diaminopyridines (calcium uptake enhancers that promote acetylcholine release).

Current Status of Treatment Approaches

In sum, the available studies with cholinomimetic agents provide the optimist with a basis of hope for future drug development, but they admittedly offer no immediate promises of providing effective therapeutic intervention. However, it must be recognized that currently available cholinergic agents suffer clear deficiencies that may contribute to their lack of efficacy. For example, as briefly discussed above (and recently reviewed by Bartus *et al.*[122]), there now exist many reasons for questioning why precursors such as choline or lecithin should provide significant efficacy in impaired aged or demented patients. Moreover, the two classes of cholinomimetics for which some positive evidence does exist (i.e., anticholinesterases and muscarinic agonists) suffer serious pharmacokinetic limitations, including very short durations of action, lack of specificity for particular targets (i.e. particular muscarinic receptor subtypes within specific brain regions), and narrow therapeutic window (i.e., narrow range of effective doses).

Additionally, presuming that the cholinergic system is not the sole contributing factor to the memory disturbance, it has been suggested that in order to achieve substantial efficacy in aged subjects, it may be necessary to reduce multiple, interactive neurochemical dysfunctions in the aged and demented brain.[150,151] Drug combination studies in animals and humans have only recently begun to generate interest but it may be heuristically noteworthy that several tentatively positive findings with such combinations have begun to appear.[152–160] The future of this more complicated approach clearly awaits the test of time and will demand exceptionally rigorous evaluation of therapeutic efficacy and clinical relevance.

FUTURE DIRECTIONS

Basic Research on Interactive Cholinergic and Non-Cholinergic Variables

Given the intellectual and methodological status of research in this area, several compelling directions for future research efforts are readily apparent. One obvious need is to characterize more precisely the cholinergic defect in the brains of aged animals and humans, and humans suffering from Alzheimer's disease. Only in this way will we gain sufficient knowledge of the similarities and differences between various subject populations, and therefore understand when it is prudent to extrapolate from one to the other, and when it is dangerous. Of more fundamental importance, only through this information can the necessary insight be obtained for rationally designing or developing an effective treatment for geriatric cognitive loss. Of course, further knowledge regarding the intricacies of cholinergic function may be required before we can fully understand the changes that occur with age or dementia. Fundamental information about basic neurotransmitter mechanisms, such as second messengers, multiple receptor subtypes, receptor conformational changes, membrane fluidity, and other phospholipid events, as well as information regarding the interaction of multiple neurotransmitter systems should be invaluable in this regard.

Additionally, a more in-depth understanding of the relationship between the primary cholinergic marker of Alzheimer's disease (i.e., loss of CAT activity) and the

primary neuropathological markers of the disease (plaques and tangles) should be developed. Although a definitive functional role has yet to be established for either of the classic neuropathological markers (in fact, they are known to exist in some degree in many completely normal, undemented aged people[151,162]), their importance in characterizing this disease has withstood the test of time. Further, they constitute a possible link between the etiology of the disease and the neurobiology of its primary symptoms.

Finally, systematic studies should be directed toward establishing a functional relationship between age-related changes in other neurotransmitter system(s), age-related memory loss, and the cholinergic dysfunctions documented. Surely, the identification and understanding of the roles played by other neurotransmitter systems in the memory loss of aging and dementia will require much work. To date, the majority of the arguments for the involvement of other systems has been based simply on the fact that changes in the markers of these systems have been observed in aged or demented brains. However, once substantiated, these observations merely satisfy the first of several steps required to demonstrate a functional role in the cognitive disturbances. They also presently fall far short of offering logical, empirically supported directions for drug development or pharmacotherapy.

Develop Characteristic-Specific Cholinergic Agents

Although admittedly simplistic, the cholinergic hypothesis nevertheless provides an important framework for directing pharmacological development and treatment. Few researchers in the area expect any cholinergic stimulant to reverse completely the cognitive dysfunction of Alzheimer's disease, let alone halt its insidious attack on the mind. Yet, epidemiological and sociological studies suggest that much human suffering could be reduced and billions of dollars saved annually simply by increasing the intellectual capacity of Alzheimer's patients to the point where self-care is possible and the need for expensive and dehumanizing institutionalization is therefore eliminated. It is from this perspective that the cholinergic hypothesis offers some hope and specific direction for attempting to find a solution.

Several shortcomings can be identified with currently available cholinergic agents, providing at least one approach for future drug development. Even accepting the potentially over-simplistic premise of the cholinergic hypothesis, it is difficult to imagine that any cholinergic agent will provide therapeutically significant effects unless it is improved in all or most of the following: greater selectivity and specificity for the end target; longer duration of action; wider therapeutic window; ready passage across blood-brain barrier; lack of peripheral side effects; no down-regulation of cholinergic activity; and extremely safe and non-toxic. How much might be gained by simply correcting these deficiencies of existing drugs remains an empirical issue that cannot yet be answered, but one that lies well within the scope of abilities to address.

Develop Reliable Animal Models of Primary Symptoms

The development and utilization of effective animal models can greatly facilitate discoveries to help understand and treat nearly any disease imaginable. Recognition of this, along with a growing concern for the consequences posed by Alzheimer's disease, has contributed to recent interest in developing animal models to study memory problems associated with that disease.[121,163,164] From the standpoint of the cholinergic hypothesis, the development of useful animal models would improve our ability to

test and/or refine the hypothesis, provide an important and efficient means of evaluating newly developed cholinergic agents, and offer a convenient means of comparing the effects of cholinometics with alternative pharmacological approaches. However, work in this area is particularly difficult, in part because of problems inherent in accurately measuring memory in animals, and in part because Alzheimer's disease seems to be a human-specific disease. Although recent studies suggest it may be possible to gain some insight into treatment approaches from data derived from aged animals,[121,163,165–167] there is no question that greater predictability might be achieved with an animal model that shares more of the characteristic neuropathology and neurochemical deficiencies found in the brains of Alzheimer's patients. Earlier attempts to artificially induce neurofibrillary tangles in animals via aluminum[168,169] have been disappointing, neither providing greater insight into the nature of the disease nor leading to more effective means of testing drugs to treat its symptoms. Other attempts to produce an animal model through injection of presumed transmissible agents may continue to hold promise, but have so far been equally disappointing.[170,171]

More recently, however, the evidence implicating severe deterioration in the nucleus basalis in Alzheimer's patients has given new momentum to the development of potential animal models of the disease. Although destruction of this brain region would certainly not be expected to produce the plaques and tangles observed in Alzheimer's patients, it nevertheless would provide an animal model that shares other CNS deficiencies associated with that disease, such as loss of cortical CAT activity, reduced cortical high affinity choline uptake, and degeneration of basal forebrain cholinergic neurons. At a minimum, destruction of the homologous brain region in animals should help determine the functional consequences of such degeneration and provide an empirical test of its possible role in the cognitive loss of Alzheimer's disease and other degenerative disorders.

Although work in this area is very new, recent studies in rodents already have demonstrated interesting and selective behavioral effects following destruction of this brain region. For example, in one comprehensive assessment, no effects of the lesion were observed on four different psychomotor tasks (intended to measure muscle strength, stamina, and coordination), on tests of shock sensitivity, or on the initial latency to respond in a one-trial, passive avoidance task.[82] However, the nucleus basalis–lesioned rats were severely impaired on retention of the passive avoidance task; the same test that revealed the most robust behavioral disturbances in aged rats.[163] Similar retention deficits following nucleus basalis lesions have been reported by others as well.[83,84] It should be noted that the effects of the lesion in this study were more severe than those noted with aging, for the nucleus basalis–lesioned animals exhibited deficits at both one hour and twenty-four hour retention intervals. Because a clear temporally related decline was not observed, it remained uncertain whether the deficit reflected disturbances in learning, memory, or both. Further, the passive-avoidance procedure is recognized as a relatively crude behavioral paradigm and its results are often open to multiple alternative interpretations.

For these reasons a second rodent experiment was performed in a new group of rats.[81] These rats were first trained to obtain food reward by visiting each of eight arms of a radial arm maze only once. Repeat visits to an arm were never reinforced and were scored as errors. Following several months of training and establishment of near perfect performance, the rats received sham lesions or lesions of the nucleus basalis. Two weeks following surgery the rats were retested on the radial arm maze task. This retesting revealed that the animals with nucleus basalis lesions possessed normal post-operative retention of the learned task (FIGURE 1). Thus, the lesioned rats not only retained their ability to run on the eight-arm maze and earn food reinforcement, but were also unimpaired in accurately going to each of the eight arms only once during

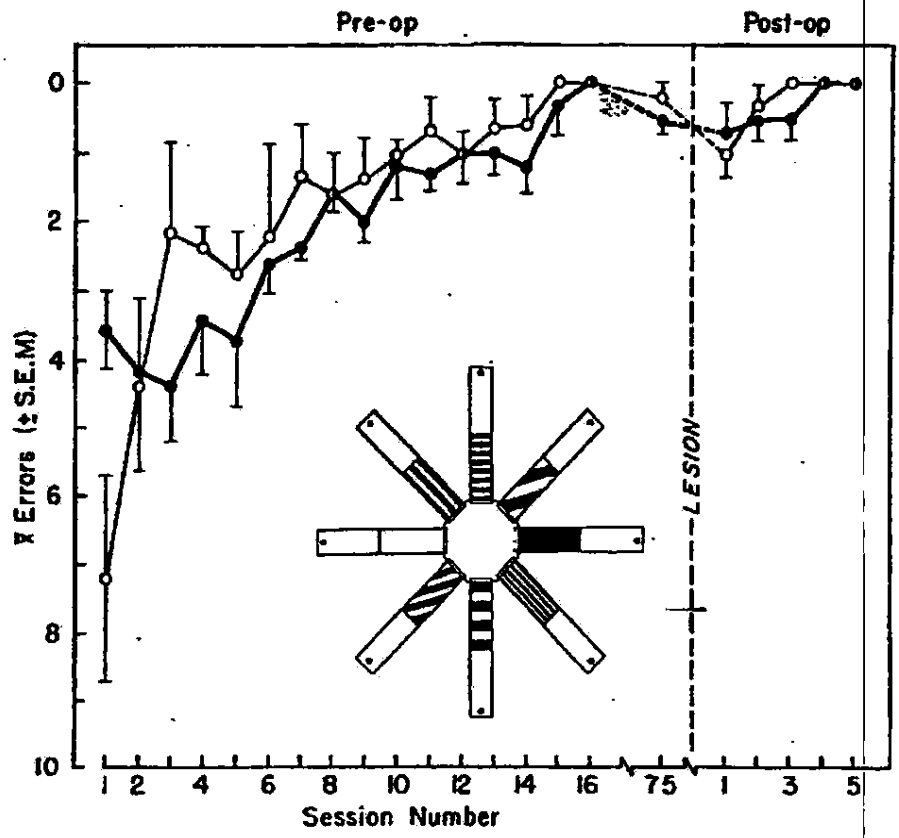

FIGURE 1. Acquisition and steady-state performance of the radial arm maze, as depicted by the mean number of errors to successfully complete all eight choices in the maze task. Repeat responses to any arm previously entered within the session are not reinforced and are treated as errors. Note no effect of nucleus basalis lesion on performance of task.

control test sessions. However, when a recent memory component was added to the task procedure, a profound deficit in the lesion group was revealed (FIGURE 2). In other words, when a retention interval was interposed between the selection of the first four arms and the remaining four arms a time-dependent decrement in performance occurred. This time-related deficit suggested that destruction of cholinergic neurons in the nucleus basalis of rats may create disturbances in recent memory analogous to those seen in aging and dementia. In addition to these lesioned young rats, aged rats, mice, monkeys, humans, and early Alzheimer's patients all exhibit memory losses that share a number of operational similarities.[121,163] Although certain quantitative differences may exist among these various conditions, members of each share a deficit in memory characterized by a somewhat preferential inability to remember brief, discrete events, with greatest deficits existing in situations where there is little or no repetition or opportunity to practice or rehearse the information to be remembered, and a time-related decline in retention, which occurs relatively rapidly (usually within minutes or hours).

The operational and conceptual similarities between the deficits produced by nucleus basalis lesions in rats and the early recent memory deficits of Alzheimer's patients were consistent with a role for this brain region in mediating memory loss of

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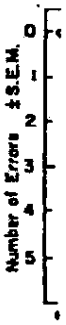

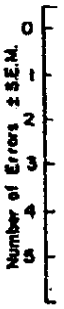

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Alzheimer's disease. However, further work with these animals revealed some of the limitations inherent in lesion procedures and cautioned that a more complex interpretation of the data was required. During the course of several months of training on the radial-arm maze task, the performance of the lesioned rats on the delay conditions gradually improved. By six months after surgery, retention was not different from the controls (FIGURE 2). Further, when trained and tested in the same passive avoidance task that earlier had revealed marked impairments from these lesions, these animals exhibited no retention deficit (FIGURE 3). Finally, following sacrifice, a series of neurochemical determinations revealed that neither cortical CAT activity nor high affinity choline uptake recovered measurably in the rats exhibiting the behavioral recovery, nor was there any hint of compensatory changes in the hippocampus or olfactory bulbs (terminal areas for parallel cholinergic pathways). Finally, no changes in muscarinic receptor density were observed in any brain region studied (TABLE 2). In summary, although severe and selective deficits in recent memory were observed following destruction of basal forebrain cholinergic neurons in young rats, complete recovery of the memory loss gradually occurred over the next several months. Further, no neurochemical correlate of this recovery could be identified.

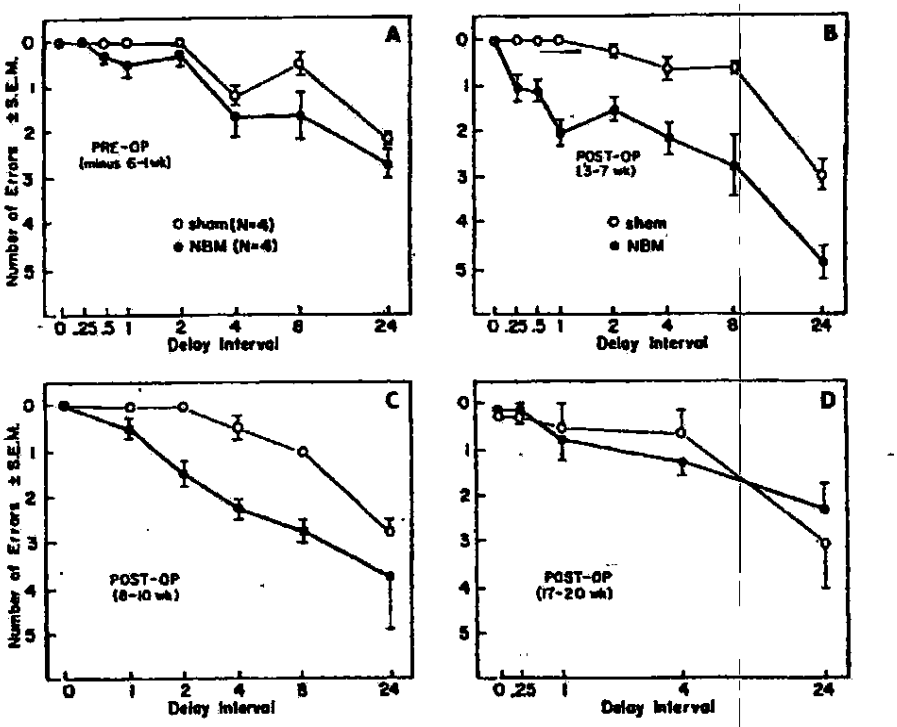

FIGURE 2. Time-dependent retention gradients established in the radial-arm maze by rats with nucleus basalis (shaded circles) and sham lesions (open circles). The gradients were established by allowing access to only four of the eight arms before the delay interval. Following variable delay intervals, all eight arms were available to assess the animals' ability to remember which arms had been visited earlier in the session. (A) Performance 1–6 weeks prior to surgery; (B) Performance 3–7 weeks following surgery; note significant effect of lesion when delay interposed between selection of first and last four arms; (C) Performance 8–10 weeks post-op, with persistence of deficit, but hint of recovery of function; (D) Performance 17–20 weeks post-op; note complete recovery of lesioned rats.

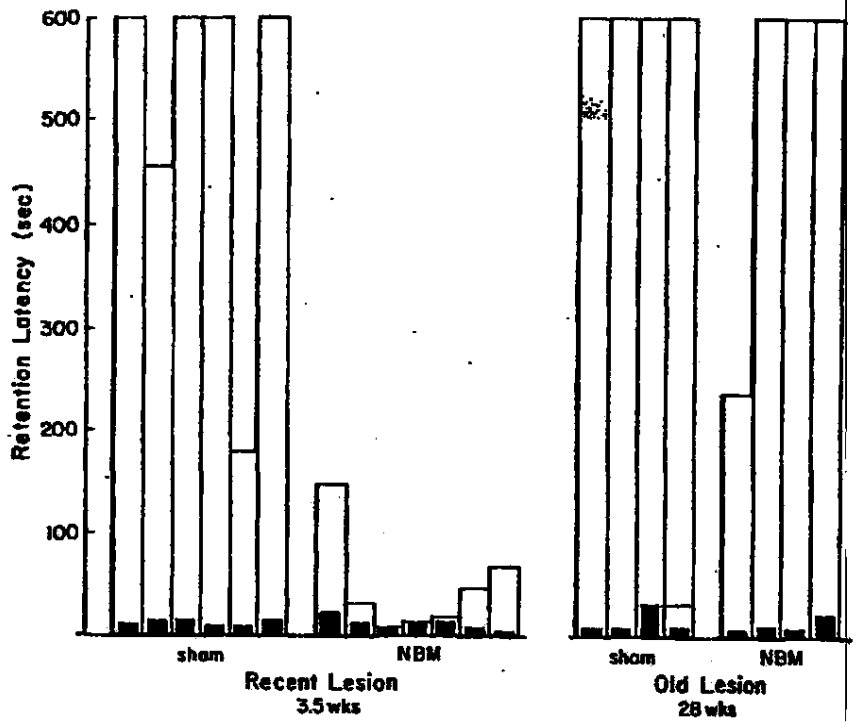

FIGURE 3. Retention of passive avoidance task within one month of NBM lesion or several months following surgery. The animals in the "old lesion" group (28 weeks post surgery) exhibited no deficit on the task and had been trained on the radial-arm maze task (as depicted in FIGURE 2) prior to training and testing on this procedure.

TABLE 2. Cholinergic Markers Determined Two Weeks (Recent) or Six Months (Long Term) Following Nucleus Basalis Lesions in Rats (Compared to Sham-Operated Controls)

		CAT Activity[a]	HACU	QNB
Frontal cortex	Recent Lesion	−46%	−32%	no change
	Long-term Lesion	−42%	−33%	no change
Parietal/temporal cortex	Recent Lesion	−36%	n.d.	no change
	Long-term Lesion	−26%	n.d.	no change
Hippocampus	Recent Lesion	no change	no change	no change
	Long-term Lesion	no change	no change	no change
Olfactory bulbs	Recent Lesion	no change	n.d.	no change
	Long-term Lesion	no change	n.d.	no change

[a]Abbreviations: CAT—choline acetyltransferase, HACU—high affinity choline uptake, QNB—specific binding of the ^{3}H-labeled, muscarinic antagonist, quinuclidinyl benzilate, and n.d.—not determined.

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The data from this study leave unanswered the question of the functional role played by degenerated neurons in homologous brain regions in Alzheimer's patients. However, in our opinion, the data clearly support the idea that this group of neurons (and their extrinsic projections to the cortex) plays an important and potentially quantifiable role in mediating recent memory. Certainly the behavioral recovery observed after six months hardly outweighs the evidence supporting an important involvement of the region in mediating recent memory. Indeed, considerable empirical evidence exists for some to predict such complete recovery of function.[172–174] Rather, the specificity and severity of memory loss strongly implicates this nucleus and pathway in mediating memory. This evidence, coupled with the operational similarities of the deficit observed to the memory loss described for aged rodent, primates, humans, and Alzheimer's patients, makes the argument even more compelling. A major question that presents itself is whether similarly complete recovery would have occurred if the lesion had been performed in aged animals who may have a reduced capacity to recover lost function. From a different perspective, aged animals with basal forebrain degeneration may represent a more accurate analogue to Alzheimer's patients. Also of interest would be the effects of combining lesions of the basal forebrain with other areas also implicated in Alzheimer's disease (such as hippocampus or locus coeruleus). Finally, the question of the functional significance of the classic neuropathology of Alzheimer's disease (i.e., tangles and plaques) must be considered; perhaps both the neuropathology and neurodegeneration must exist to cause a severe and permanent loss of cognitive function.

The question of species suitability for these studies is another issue deserving some comment. Although the ventrolateral globus pallidus is commonly agreed to represent an area homologous to the primate nucleus basalis of Meynert,[73,75,76] the region is poorly defined in rodents and certain differences in topographical projections and cellular distribution may exist. Further, the nature of the specific memory loss impaired with age and dementia continues to present problems when studied in rodents. Alternatively, the similarity of structure and organization of the basal forebrain nuclei in human and non-human primates, combined with the relative similarity of behavioral repertoire and cognitive test capabilities in these species, greatly reduces the assumptions necessary to extrapolate from the effects of lesions in monkeys to the functional consequences of degeneration of the basal forebrain nuclei in aged, demented humans.

Recent accounts of the first studies with non-human primates have been equivocal. For example, using a delayed, non-matching task, Aiger *et al.*[175] reported that lesions of the nucleus basalis failed to significantly impair memory, but that reliable deficits in comparison to controls were observed when the subjects were given a normally low dose of anticholinergic. On the basis of these data, it has been concluded that destruction of that brain region alone is not sufficient to cause significant memory loss in primates. However, such a conclusion rests on the somewhat tenuous logic of accepting the null hypothesis based on a single behavioral paradigm that used few subjects, lesions without histological confirmation, and no independent demonstration of task validity. Clearly, additional systematic work is required before any gross generalizations can be made. Future experimental work in both primates and rodents, as well as with postmortem tissue from various demented and non-demented patient populations, should help clarify the role of this brain region in mediating behavior and its relationship to the cognitive loss associated with aging and dementia.

Although the development of a valid animal model of Alzheimer's disease could prove invaluable in helping to identify effective pharmacological treatments for the cognitive symptoms of this disorder, it is also likely that the answers to questions raised during the development of such animal models will prove to be equally useful. In

addition to their more glamorous and optimistic intentions, it is in areas such as this, that the direction offered by concepts like the cholinergic hypothesis demonstrate their worth as viable scientific contributions.

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